

## Selected WFSOS Abstracts

### 1. Concomitant Accelerated Radiochemotherapy as Neoadjuvant Approach to Rectal Cancer: A Pilot Study

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**Background and Objectives:** Neoadjuvant treatment in rectal cancer is supposed to improve local control, reducing tumor bulk; this would probably lead to a higher rate of sphincter-sparing operations and an increased disease-free survival. The aim of the present prospective study was to evaluate the feasibility of a new protocol of accelerated radiochemotherapy.

**Methods:** Forty patients with histologically proven rectal cancer were enrolled in the study. They had a  $\geq$  T2 lesion at clinical examination and endoscopic ultrasound. Preoperative radiotherapy was delivered with linear accelerator, patients receiving 45 Gy by using a "box" or "three fields" technique with two daily fractions (interval: 6 hr) of 1.8 Gy for 5 days in 13 days. Concomitant intravenous 5-FU was given at a dose of 300 mg/mq/day. Acute toxic effects were evaluated on a weekly basis; late toxic effects were recorded at 6 months intervals.

**Results:** Clinical staging was as follow: T2-8, T3-25, T4-7. Endoscopic ultrasound staging was uT2-10, uT3-22, uT4-8. Median distance from the anal verge was 6.6 cm; median tumor size was 4.2 cm. Four weeks after radiochemotherapy, patients underwent surgical treatment consisting of 5 (13.1%) abdominoperineal resections; 32 (84.2%) anterior/low anterior resections; one patient had no resection. A diverting colostomy was performed in 19 cases. Two patients had no operation because of complications of radiotherapy (small-bowel obstruction) and myocardial ischemia. Usual surgical morbidity was not increased by preoperative treatment. One postoperative death was observed. Preoperative treatment produced a complete response (CR) in 12 cases (33%). In two cases there was no trace of the tumor in the specimen but pericolic lymph nodes were metastatic. Pathological downstaging occurred in 31 cases (83.7%); no response was found in 6 (17.3%). Median follow-up time was 13 months (range, 3–22). One local recurrence (pelvic disease) has been detected up to date. Acute and late toxicity rates were in keeping with previously reported experience with daily single fractions.

**Conclusions:** The rationale to accelerate radiotherapy schedule is to avoid the early local recurrence after surgical treatment, these being the majority of all recurrences. The innovative aspect of the proposed schedule is the double daily fraction, with a 50% reduction of the overall treatment time compared to the conventional schedules.

### 2. Metastasectomy for Recurrent Stage IV Melanoma

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Many patients undergoing complete surgical resection of stage IV melanoma ultimately develop recurrent disease. We examined whether a second metastasectomy prolongs survival in patients with recurrent stage IV melanoma. Retrospective review of our 8,000-patient melanoma database identified 211 patients treated by complete surgical resection of stage IV metastases from 1970 to 1995. The 131 patients who developed recurrent stage IV disease (minimum follow-up, 24 months or death) comprise the study population. The median time to develop recurrent stage IV disease was 8 months (range, 0.6–91.8 months). The median number of involved anatomic sites was one (range, 1–3), including soft tissue (47%), lung (21%), brain (12%), GI (11%), and bone (8%). From the time of treatment for recurrent stage IV melanoma, the median survival in patients undergoing a complete surgical metastasectomy was 17.4 months, compared with 12.6 months and 5.7 months in those undergoing a palliative surgical procedure and nonsurgical management, respectively. The 5-year survival

for patients in the complete surgical metastasectomy group was 19.2%, compared to 6.0% and 2.0% for those in the palliative surgical and non-surgical groups, respectively. By multivariate analysis, the two most important prognostic factors for survival following diagnosis of recurrent stage IV melanoma were a prolonged disease-free interval to recurrence ( $P < 0.0001$ ) and complete surgical metastasectomy of the recurrence ( $P < 0.0001$ ). Metastasectomy can prolong survival in recurrent stage IV melanoma patients provided the patient can be surgically rendered disease-free.

### 3. Diagnostic and Therapeutic Implications of Sentinel Node Mapping in Colorectal Cancer: A Prospective Study

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**Background and Objectives:** Routine histological examination may miss nodal micrometastases in patients with colorectal cancer and thus may understage some patients who may otherwise benefit from adjuvant chemotherapy. Sentinel lymph node (SLN) mapping for melanoma and breast cancer have greatly enhanced the diagnosis of micrometastases. The purpose of this study is to see if SLN mapping technique could be used in colorectal cancer and to find its implications in final diagnostic staging for appropriate therapeutic intervention.

**Methods:** Thirty consecutive patients with proven or suspected colorectal cancer were studied for SLN mapping. At operation, 0.5–1 cc of Lymphazurin (1%) was injected into the subserosal layer around the palpable tumor. The first 1–3 blue nodes identified during the mobilization were marked as SLNs. Following this, a standard resection with en bloc regional lymphadenectomy was done. If an SLN was identified outside the area of standard operation, an extended resection was carried out. Meticulous pathological examination of these nodes in addition to the entire specimen was done.

**Results:** There were 25 colon/5 rectal cancer patients; ages ranged from 36 to 95 years, with 17 males and 13 females. The SLN was successfully identified in 29/30 patients (97%). There were a total of 468 lymph nodes examined (16/patient), of which a total of 40 (1.3/patient) designated as the follows: one SLN in 19 patients; two SLNs in 9 patients; and three SLNs in 1 patient. In 21/22 (95%) patients of whom the SLNs were without metastases (negative), all of the non-SLNs also were negative. In eight patients (27%), SLNs were positive for metastases. In four of eight (50%) of these patients, other non-SLNs also were positive in addition to the SLN. In the other four (50%) patients, the SLNs were the only site of metastases, with all other non-SLNs being negative. In two of these four patients, metastases were identified only after multiple microsections of a single SLN. One patient with low rectal cancer with preoperative chemo- and/or radiotherapy failed to show any SLNs but was found to have metastases in 1/43 lymph nodes, thus being the only skip lesion in the entire series (3.3%). In another patient with two closely situated primary tumors, SLNs were negative for metastases, but non-SLN adjacent to the tumor was directly invaded by the tumor, thereby having false negative results in 1/29 (3.4%) cases. Finally, in two patients, SLN mapping demonstrated aberrant lymphatic drainage, thus altering the extent of resection.

**Conclusions:** SLN mapping can successfully predict presence or absence of lymph node metastases in colorectal cancer in 28/30 (93.3%) of cases. Additional lymph node metastases beyond the usual site may be identified and thus may alter the surgical resection margin. In 4/30 (13.3%), the SLN was the only site of metastases. This may have upstaged these patients, who could then potentially benefit from implementation of adjuvant chemotherapy.

#### 4. Anti-CEA-Scintigraphy With CEA-Scan Versus Probe-Guided Surgery for Colorectal Cancer

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**Background and Objectives:** Immunoscintigraphy (IS) is known to be highly accurate in the diagnosis of primary and recurrent colorectal cancer. The aim of this study was to compare the results of IS to the findings of scintimetry during probe-guided surgery (PGS).

**Methods:** The prospective study comprises 20 patients with endoscopically and histologically verified colorectal tumors in stages IA through IIIB. They were submitted to IS with CEA-Scan. This radiopharmaceutical consists of 1 mg of a fab—monoclonal antibody fragment to CEA, labeled with 25 mCi of  $^{99m}\text{Tc}$ . Planar and SPECT images were taken after 1 and 5 hr, respectively. The patients were operated on 24 hr later. Scintimetry with a C-Trak probe, a handheld gamma detector, was performed immediately after laparotomy.

**Results:** While IS detected 19 of the 20 known primaries, they were all confirmed by the probe which, in addition, found a synchronous cancer in the ascending colon of a patient with known rectal carcinoma. Involved N1 nodes were detected in two patients by IS vs. in four patients by C-Trak. The probe identified metastatic N2/3 nodes in four patients, while IS was positive in only one. As patients with known distant metastases were excluded from PGS, IS did not detect liver metastases in one and peritoneal carcinosis in another patient. Both were confirmed by the probe. While IS—still far superior to the conventional radiological workup—had identified 22/31 cancerous lesions, all 31 foci were found with the probe and then confirmed by pathology. Scintimetry led to an intraoperative upgrading in 6/20 patients.

**Conclusions:** The results of intraoperative immunoscintimetry with a  $^{99m}\text{Tc}$ -probe are significantly better than those of every preoperative staging procedure, including IS. PGS turns out as a first promising step toward stage-adjusted surgery for colorectal cancer.

#### 5. Accuracy of Lymphoscintigraphy in Indicating the Number of Sentinel Lymph Nodes in Patients With Melanoma

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This study was undertaken to establish the incidence, the nature, and the cause of discrepancies between the number of sentinel (first-echelon) lymph nodes indicated by lymphoscintigraphy and the actual number of sentinel nodes recovered during surgical exploration. Lymphoscintigraphy was performed with flow imaging and static imaging at 2-hr postinjection of 60 MBq  $^{99m}\text{Tc}$ -nanocolloid in 168 patients with clinically localized primary melanoma of the skin. The following day, sentinel nodes were retrieved intraoperatively with the vital dye technique and with a gamma detection probe (Neoprobe 1000). Lymphoscintigraphy showed drainage to a total of 346 sentinel nodes in 211 lymphatic fields. In 40 lymphatic fields (19%), a different number of sentinel nodes was found during the operation. In one patient, a preoperatively well-visualized sentinel node could not be retrieved. Vital dye indicated the correct number of sentinel nodes in 64% of the discrepancies, and the gamma detection probe in 36%. Discrepancies

were due to the limited resolution of the gamma camera (80%), a lymphatic plexus mistaken for a sentinel node (10%), lymphatic drainage to the opposite ends of a single elongated node (7%), and lack of drainage of the tracer to the sentinel node (2%). Although lymphoscintigraphy is indispensable for lymphatic mapping, the predicted number of sentinel nodes is accurate in only 81% of cases. Intraoperative use of both vital dye and a gamma probe is of crucial importance.

#### 6. Lymphatic Mapping and Sentinel Node Biopsy in Breast Cancer

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**Background and Objectives:** The possibility to identify the sentinel lymph node (SN), as demonstrated in cutaneous melanoma, might avoid also in breast cancer the systematic axillary dissection in clinically node negative (N0) patients with pathologically negative SN (SN<sup>-</sup>); conversely, axillary dissection should be performed in patients with clinical evidence of node metastasis (N1 or more) or with pathologically positive SN (SN<sup>+</sup>). A pilot study was undertaken in patients with stage I–II breast cancer to identify SN by means of Patent Blue V peritumoral injection with the aim of evaluating the selectivity of the lymphatic drainage in SN related to the primary site, and the likelihood of metastases within SN as compared to nonsentinel nodes (nSN).

**Methods:** From May 1996 to May 1997, 55 patients (age, 40–84 years; median age, 65 years) underwent SN detection at the Division of Surgical Oncology (IST, Genoa). Following induction of general anesthesia, 0.5–1 ml of Patent Blue V was injected in the peritumoral area; after tumorectomy and intraoperative histological confirmation of invasive carcinoma, an axillary incision was performed to identify the SN, corresponding to the first lymph node draining a blue-dyed lymphatic channel. The surgical procedure was always completed with radical axillary dissection.

**Results:** SN was identified in 36 of 55 patients (65.4%) after a median lap of 20 min from dye injection: 28 of 36 patients were N0, and 9 of them had lymph node metastases at pathologic assessment (pN<sup>+</sup>). In five patients, the SN was the only site of metastases (SN<sup>+</sup>); in three patients, SN<sup>+</sup> was associated with metastases in nonsentinel lymph nodes (nSN<sup>+</sup>), and there was a single case of pathologically negative SN (SN<sup>-</sup>) with one nSN<sup>+</sup> (false negative rate, 1/9, or 11.1%). Eight of 36 patients were N1 and 4 were pN<sup>+</sup>: 2 patients had SN<sup>+</sup> as well as nSN<sup>+</sup>, and 2 had SN<sup>-</sup> with nSN<sup>+</sup> (false negative rate, 2/4, or 50%). On the whole, 474 lymph nodes were examined in 28 N0 patients with detected SN: 9 SN<sup>+</sup> were found among 30 SN (30%) (2 SN in 2 patients); 7 nSN<sup>+</sup> were observed among 447 nSN (1.5%), with only one nSN<sup>+</sup> as the sole site of lymph node metastases (false negative rate, 1/447, or 0.2%). As regards 8 N1 patients, 130 lymph nodes were examined in the operative specimen: 2 SN<sup>+</sup> were detected among 8 SN (25%); 13 nSN<sup>+</sup> were observed among 122 nSN (10.6%), with 2 nSN<sup>+</sup> as the sole site of lymph node metastases (false negative rate, 2/122, or 1.6%).

**Conclusions:** These findings seem to confirm the feasibility to identify selectively SN in patients with operable breast cancer (30 SN in 28 N0 patients; 8 SN in 8 N1 patients); moreover, an elective localization of lymph node metastases occurred within SN; in fact, lymph node metastases in N0 patients were 20-fold more likely in SN as compared to nSN (30% and 1.5%, respectively), while in N1 patients this rate was almost threefold (25% and 10.6%, respectively)

## 7. Diagnosis of Occult Micrometastases in Oral Cancer With Sentinel Lymph Node Biopsy

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In oral cancer, the incidence of lymph node metastases varies according to tumor size and is about 20% in T1 and over 50% in T2. The treatment of choice for all patients with clinically palpable node metastases is a locoregional lymphadenectomy, while its efficacy is still controversial in patients with N0 lymph node clinical status. This article reports the initial experience of a multicenter trial with a new technique to detect occult micrometastases by sentinel lymph node biopsy (SLB). From January 1996 to June 1997, 18 patients with oral cancer cavity tumors were submitted to SLB. There were 14 (77.8%) males and 4 (22.2%) females with an age ranging from 39 to 72 years and a median of 55.5 years. All patients were staged with routine biochemical and instrumental procedures, in particular with ultrasound and computed tomography of the neck to reveal unknown lymph node metastases. Lymphoscintigraphic study was also performed to identify the locoregional drainage basin that was marked with a cutaneous pen for an easier surgical identification. Surgical procedure was realized according to Morton technique with perilesional injection of Patent Blue V 20 min before cutaneous incision. All patients were submitted to a complete lymphadenectomy associated with the excision of the primary tumor. Sentinel lymph node were identified in 15 (83.3%) cases and in 2 (13.3%) cases frozen section examination revealed micrometastatic disease. Definitive histopathological stain after modified radical neck dissection found three (20%) patients with secondary lymphatic localization. Fourteen (77.8%) were alive, disease-free, with a follow-up ranging from 1 to 20 months. One death was due a rapid neoplasm diffusion. Feasibility and reliability of this new procedure might still have to be demonstrated, but our results suggest a possible therapeutic benefit.

## 8. Sentinel Lymph Node Biopsy in Early Diagnoses of Stage III Cutaneous Melanoma

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The treatment of cutaneous malignant melanoma has been changed in the last 4 years after the introduction of sentinel lymph node biopsy technique, which permits identification of occult lymph node micrometastases. This article reports the experience of the Division of Surgery "B" of National Cancer Institute of Naples in the treatment of stages I and II of cutaneous melanoma with this new procedure. From January 1995 until July 1997 in our institution, 150 primary melanomas were diagnosed and 54 of them were submitted to sentinel lymph node biopsy (SLB) according to Morton technique. Included in this study were 22 (40.7%) males and 32 (59.3%) females, with an average age of 47.5 (range 19–76) years. There were 16 (29.6%) patients at stage I, 29 (53.7%) at stage II, and 9 (16.7%) at stage III; anyone presented at diagnoses with a clinically palpable lymph node. Primary malignant melanoma was located in 32 (59.2%) cases at trunk, in 21 (38.9%) at extremities (6 upper and 15 lower), and in 1 case in the neck. Thirty-six patients were studied with lymphoscintigraphy locoregional site drainage identified in 32 (88.9%). In four cases with no

lymphatic drainage identified at lymphoscintigraphy, only wide excision of primary lesion was performed. Fifty (92.5%) patients were submitted to SLB with intraoperative perilesional intradermic injection of Patent Blue V. In 43 (86%) cases, a lymph node was identified; the others were analyzed with frozen section, H&E stain, and in 10 (20%) a lymph node micrometastases were found. Three cases were positive only at immunohistochemical staining (HMB-45/S-100). All patients with positive metastatic nodes were referred for a complete lymphadenectomy. The follow-up varies from 1 to 31 months and only three (6%) patients with SLB-negative developed locoregional node disease after 5, 6, and 13 months, respectively. All the others are alive and disease-free. These results suggest sentinel lymph node biopsy to be an accurate and easy method to detect occult micrometastases in primary malignant melanomas, identifying those patients that might benefit from a complete lymphadenectomy.

## 9. Efficacy of Selective Dissection of Regional Nodes in Patients With 1.5-mm or Thicker Melanoma of the Trunk

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We recently reanalyzed the WHO Melanoma Programme Trial 14 that was designed to evaluate the efficacy of elective regional node dissection in patients with a primary melanoma on the trunk and a tumor thickness of 1.5 mm or greater. Two hundred fifty-two patients entered into the study; 122 of these were randomized to receive immediate node dissection and 118 have wide excision and dissection delayed until time of appearance of clinically detectable node metastases. Patients submitted to wide excision only as primary treatment had survival rates of 50.5% and 40.4% at 5 and 10 years, respectively, while 5- and 10-year survival rates in patients who received immediate node dissection were 61.7% and 48.3%, respectively. The difference is not statistically significant ( $P = 0.09$ ). No subgroups of patients identified by prognostic criteria of the patient and of the primary melanoma had benefit from elective node dissection. Patients with occult regional node metastases had 44.2% 10-year survival rate and patients in whom the regional node dissection was delayed at the time of appearance of regional node metastases had a 10-year survival rate of 20.6% ( $P = 0.04$ ). Multivariate analysis of survival showed that the routine use of immediate node dissection had no impact on survival ( $P = 0.07$ ), while the dissection delayed at the time of appearance of regional node metastases adversely affected survival ( $P = 0.005$ ). The survival observed in patients with histologically negative nodes submitted to elective node dissection was not different from the one observed in patients who did not develop node metastases after wide excision of primary melanoma ( $P = 0.63$ ). The results of this study confirm the curative role of surgical treatment of clinically undetectable node metastasis and support the introduction of clinical procedures such as sentinel node biopsy and selective dissection aimed at early detection of metastatic deposits in regional lymph nodes. Until the results of the ongoing international randomized study aimed at assessing the efficacy of selective lymphadenectomy are available, these features could have important implications for regional node management in patients with cutaneous melanoma, finally settling the debate between advocates and opponents of elective lymphadenectomy.



### 10. Sentinel Node Biopsy in Vulva Carcinoma

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In patients with early stage squamous cell cancer (SCC) of the vulva, an inguinofemoral lymphadenectomy is primarily performed as a diagnostic procedure. The morbidity of this procedure, however, is not negligible. The aim of the present study was to evaluate the feasibility of minimally invasive detection of the sentinel groin lymph node (SGLN) and to investigate if the histopathology of the SGLNs is representative of the other non-SGLNs. Patients with early stage SCC of the vulva, planned for resection of the primary tumor and uni- or bilateral inguinofemoral lymphadenectomy, were eligible for our study.  $^{99m}\text{Tc}$ -labeled colloid was injected intradermally around the tumor on the day before operation. Images were recorded immediately and after 2.5 hr, using a digital gamma camera. SGLN locations were marked on the overlying groin skin. On the next day, following induction of anesthesia, Patent Blue V was injected intradermally around the tumor. At the operation, SGLNs were identified using a handheld gamma detection probe. It was noted if SGLNs were found by the probe, by Patent Blue V, or by both techniques. After resection of the SGLNs, a standard inguinofemoral lymphadenectomy was performed. The histopathology of the SGLNs was compared with the non-SGLNs. The procedure was well tolerated by 10 out of 11 patients. One patient refused the injection of colloid because of anxiety for pain. In all 10 patients, identification of the SGLNs was successful. Mean time for identification was 11 min. Identification of SGLNs was mainly by the probe. Ten of 18 removed SGLNs were also blue-stained (56%). In eight patients, both SGLNs and non-SGLNs were negative. Two patients with positive SGLNs also had other positive non-SGLNs. Our study shows that identification of SGLNs in SCC of the vulva is feasible with the combination of  $^{99m}\text{Tc}$ -labeled colloid and Patent Blue V. So far, no false negative SGLNs have been found, but expansion of the study is necessary to determine the possible clinical application of this diagnostic technique.

### 11. Staging Early Lymphatic Metastases in Melanoma: The Case for Superselective Lymph Node Dissection

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**Background and Objectives:** In 236 patients with clinical stage I melanoma, sentinel node (SN) biopsy detected occult lymph node metastases in 50 of 250 mapped basins (20%). Two patients refused completion lymphadenectomy. In the 48 subsequent lymph node dissections (LND), additional metastases were found in only 12 cases (25%). The morbidity of groin or neck dissection in particular is considerable, while there is still no evidence that (s)elective LND affects long-term survival. We studied the size and distribution of tumor metastasis within the SNs to determine possible parameters that may predict the extent of lymphatic dissemination.

**Methods:** All SNs were additionally subjected to serial sectioning and immunohistochemical staining using S-100 and HMB-45. The largest surface area of (all) metastatic foci in any one of the SN sections was determined morphometrically. Established prognostic primary tumor factors, such as Breslow thickness, ulceration, and lymphatic invasion, were included in the model.

**Results:** The size of the micrometastases in the SN varied from 0.0005 to 13.96 mm<sup>2</sup>. Distribution of tumor ranged from tiny clusters in the marginal sinus to extensive infiltration of the entire lymph node. In 36 of 48 lymph nodes (75%) only the SN was positive, while in 12 (25%) there were additional metastases in the lymph node. By correlating SN metastasis area to primary tumor Breslow thickness, it was possible to set limits for a positive lymph node: no patient with a Breslow <3.0 mm and area <0.3 mm<sup>2</sup> had more positive nodes. In 18 patients, other unfavorable factors were present: 10 showed ulceration, 4 had lymphatic invasion in the primary tumor, 2 patients were pregnant, and 1 was under chemotherapy for concurrent disease. If these patients are excluded, the limits for a positive lymph node can be increased to a metastasis area of 1 mm<sup>2</sup> for any Breslow thickness.

**Conclusions:** Using this simple staging system, it may be possible to predict the extent of early lymphatic spread. Based on primary tumor characteristics and morphometry of the SN metastasis, a policy of superselective lymph node may become feasible, avoiding unnecessary morbidity while providing refined prognostic parameters.

### 12. Outcomes of Combination Gene Therapy in a Murine Model for Colorectal Carcinoma

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Expression of the herpes simplex virus type 1 thymidine kinase (HSV1-TK) gene results in tumor regression following the administration of ganciclovir (GCV). Tumor regression is mediated by the generation of an antitumor immune response. The aim of this study was to determine if the treatment of HSV1-TK expressing tumors resulted in antitumor immune response. The MC26 colon carcinoma cell line was transduced in vitro with the HSV1-TK or interleukin 2 genes. Subcutaneous tumors were generated by the injection  $1 \times 10^6$  cells in BALB/C mice. Tumors were allowed to grow for 7 days; animals were treated with intraperitoneal GCV for 5 days. Tumor volumes were determined. In protocol 1, animals were divided into the following groups: group 1: MC26TK (GCV); group 2: MC26TK (saline); group 3: MC26 (saline). Control animals (group 3) generated subcutaneous tumors with a mean volume of 250 mm<sup>3</sup>. Treated animals (group 1) showed tumor regression with a mean tumor volume of 7.5 mm<sup>3</sup> ( $P < 0.001$ ). In the absence of drug selection, tumor regression did not occur (group 2) and mean tumor volume was 350 mm<sup>3</sup>. In protocol 2, subcutaneous tumors were generated using mixed cell populations. Animals were divided into the following groups: group 1: 100% MC26 (saline); group 2: MC26:MC26TK (GCV); group 3: MC26:MC26IL-2 (saline); group 4: MC26TK:MC26IL-2 (saline); group 5: MC26TK:MC26IL-2 (GCV); group 6: 100% MC26IL-2 (saline). Control animals (group 1) generated tumors with a mean volume of 406 mm<sup>3</sup>. Treated animals (group 2) showed tumor regression, mean tumor volume 53 mm<sup>3</sup> ( $P < 0.01$ ). Combination therapy (group 5) resulted in enhanced regression with a mean tumor volume of 30 mm<sup>3</sup> ( $P < 0.01$ ), although this failed to reach significance when compared to group 2. Expression of IL-2 (group 6) resulted in reduced tumorigenicity, mean tumor volume 209 mm<sup>3</sup> ( $P < 0.05$ ). In group 4, expression of the TK protein in the presence of IL-2 failed to result in tumor regression and had a mean tumor volume of 387 mm<sup>3</sup> compared to group 3 mean tumor volume of 249 mm<sup>3</sup>. In all the above groups, there was no significant regression of an MC26 tumor on the opposite flank. In addition, T-cell cytotoxicity assays failed to identify a cytotoxic T-cell population.

### 13. Radical Abdominopelvic Lymphadenectomy for Rectal Cancer

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The presence of pelvic lymph node metastasis including the lateral pelvic lymph node has been reported as 9%–18%, which might be a cause of local recurrence after curative resection of rectal cancer. Recently, total mesorectal excision with complete autonomic nerve preservation was reported to have good local control. The aim of this study was to assess the frequency of upward and lateral lymph node metastasis beyond the dissection plane of total mesorectal excision in rectal cancer. We performed radical abdominopelvic lymphadenectomy in consecutive series of 150 patients with rectal cancer between January 1996 and June 1997 and reviewed the medical records retrospectively. We analyzed the frequency of metastasis of upward and lateral lymph node according to the distance from the anal verge and depth of invasion. There is no difference in the frequency of positive lymph nodes according to the level of the tumor. The frequency of lymph node metastasis according to the depth of invasion was T1 (mucosa and submucosa) 0/11, T2 (confined to proper muscle) 2/29 (7.8%), T3 (perirectal fat invasion) 50/93 (53%), T4 (adjacent organ invasion) 4/7 (57%). The site of lymph node metastasis was pararectal 70/150 (47%), paraaortic 6/150 (4%), the origin of inferior mesenteric artery 2/150 (1.3%); no metastasis was found at the aortic bifurcation, internal iliac, external iliac, or the middle rectal artery site. The common iliac artery lymph node 3/65 (4.6%), obturator lymph node 1/16 (6.2%), presacral or promontory 5/29 (17.2%) showed metastasis. The upward lymph node metastasis along the inferior mesenteric artery and paraaortic area was rectosigmoid (9.3%), upper rectum (7.6%), midrectum (4.9%), lower rectum (4.3%). The lateral pelvic lymph node metastasis was upper rectum (15.3%), midrectum (2.5%), lower rectum (4.3%). The upward and lateral lymph node metastasis in T1 and T2 was none, whereas T3 shows upward (8.6%) and lateral (5.3%). We found that there was no upward and lateral pelvic lymph node metastasis beyond the dissection plane of total mesorectal excision in T1 and T2 rectal cancer, but the possibility of lymph node metastasis at the upward and lateral direction is still present in T3 or T4. So the appropriate application of radical abdominopelvic lymphadenectomy for curative resection of the rectal cancer will be needed for decreasing local recurrence.

### 14. The Role of Surgery in the Therapy of Gastric Lymphoma

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Despite a large number of publications within the last few years, it is undoubted that many questions concerning non-Hodgkin lymphoma of the gastrointestinal tract still have to be answered. We present some preliminary results of a prospective multicenter trial from Germany. Up to January 1997 data from 403 patients suffering from gastric lymphoma were collected from 154 hospitals.

Treatment included operation on the one hand and radiation (depending on stage and grading IF 30 Gy and 10 Gy Boost or 40 Gy abdominal bath) and/or chemotherapy (CHOP or MCP) on the other hand. Ninety-nine patients with gastric lymphoma were operated (male:female ratio, 1.5:1; mean age, 56.5 years; range: 19–81 years). Although all patients underwent preoperative upper gastrointestinal endoscopy, the diagnosis was known in only 61/99 patients at the time of operation. The most frequent operative procedure was partial or total gastric resection with or without lymph node dissection. According to the Musshoff classification, 38 patients (38%) were classified stage IE, 36 patients stage IIIE (36%), 13 patients stage II2E (12%), 6 patients stage IIIE (7%) and stage IVE (7%). In only 46% (46 patients), a curative R0 resection could be achieved. Until now there is no significant difference in survival between the operated patients and those who were treated by chemotherapy or radiotherapy (log rank test,  $P = 0.64$ ). Our conclusion is that at the moment there is no gold standard in the therapy of gastric non-Hodgkin lymphoma.

### 15. Validation of a New Staging System for Curatively Resected Colorectal Adenocarcinoma (CRAC)

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**Background and Objectives:** The aim of the study was to validate a new classification of curatively resected colorectal adenocarcinoma (CRAC) that is more predictive of personal prognosis, and on which personalized, cost-effective postoperative management and follow-up may be planned.

**Methods:** Two hundred thirty-one curatively resected American CRAC patients were retrospectively staged according to a new four-group classification based on statistical analysis of 363 curatively resected Israeli CRAC patients. In both series the new classification was compared to the Dukes, Astler-Coller, and TNM systems.

**Results:** The new classification is based on venous invasion, depth of primary tumor penetration, and regional lymph node status. Staging the American patients by the new classification duplicated the results of the Israeli series almost identically. In both series the four stage groups differed significantly in both rate of and time to tumor recurrence and cancer-related death. Prediction of personal prognosis was improved as compared to the Dukes, Astler-Coller, and TNM staging systems, most probably due to the incorporation of the microscopic forerunner of distant, hematogenous spread, i.e., venous invasion. Groups of high-risk node-negative patients were defined, and node-positive patients were prognostically subdivided. Selection for adjuvant systemic therapy was refined. Active follow-up was unnecessary for 23.4% of patients (group 1) and may be delayed until 10–12 months postoperatively for another 39.4% of patients (group 2).

**Conclusions:** This new classification is simple, easy to use, requires no sophisticated equipment or tests, and is applicable in any health care system. We recommend it for the staging and cost-effective individualized postoperative management of curatively resected CRAC.

## 16. Is Thoracoscopy Useful in Total Esophagectomy for Esophageal Cancer?

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**Background and Objectives:** A nonrandomized study of thoracoscopy in esophageal cancer was initiated in 1992 to evaluate this technique and its interest in esophageal cancer.

**Methods:** Fifty-five patients with esophageal cancer were included in the study, with 41 males and 14 females and a mean age of 59. The tumor was located in the middle third in 48, the lower third in 4, the upper third of the esophagus in 3. Forty-eight were epidermoid and 7 were adenocarcinoma. The TNM classification was used to evaluate the local and regional spread of the tumor. The last 15 patients were studied by echoendoscopy. All patients were scored using ASA classification. All patients were treated by total esophagectomy with gastrophasty in 51 coloplasty in 4 (because of previous gastric surgery). The thoracoscopic step was done with the patient in left lateral position. Five ports were usually necessary. After cutting the right mediastinal pleura, the azygos vein was dissected, stapled, and divided with vascular Endo GIA. The esophagus was freed progressively by removing all the surrounding tissue and lymph nodes. All esophageal vessels were clipped and divided. At the end of the procedure, the esophagus was completely freed up and practically all lymph nodes were removed. After completion of the gastric tubuloplasty, the esophagus and the gastric tube were pulled up through a left cervical incision and the esogastric anastomosis was done.

**Results:** Mean thoracoscopic time was determined to be 75 min (6–210 min); mean ICU stay, 1.2 days; and mean hospital stay, 12.5 days. Operative and perioperative mortality was 5.4% (in T3 N<sup>+</sup> patients). Morbidity included one esogastric anastomotic leakage, one localized transplant necrosis both healed by local irrigation, one thoracic duct wound, four hoarseness, and six lobar atelectasias. Survival included eight patients who died in the first 13 months. Fifteen patients are alive with mediastinal or coliac recurrences or metastasis 7 to 15 months after operation. Thirty-two are alive and apparently disease-free 6 to 40 months after operation.

**Conclusions:** Compared to historic series of esophageal cancer treated by thoracotomy or transhiatal esophagectomy, the thoracoscopic approach doesn't modify the survival rate but lessens the operative time, ICU stay, pulmonary morbidity, recurrent nerve paralysis, and increases postoperative comfort of the patient.

## 17. Omega-3 and Omega-6 Fatty Acids Alter Endothelial Adhesion of Human Colorectal Carcinoma Cells

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Diets rich in  $\omega$ -6 fatty acids have been shown to promote metastases in murine tumor models, while  $\omega$ -3 fatty acids are protective. These effects may be due to alterations in the adhesion of human colorectal carcinoma (HCRC) cells to endothelial cells, an important step in the metastatic cascade. The purpose of this study was to alter the membrane-free fatty acid composition of HCRC cells in vitro and determine whether this alters their adhesion to hepatic sinusoidal endothelial cells (HSE). CX-1, a moderately differentiated HCRC cell line shown to produce hepatic metastases in an intrasplenic injection model, was treated with docosahexanoic acid ( $\omega$ -3) or linoleic acid ( $\omega$ -6). Gas chromatography was used to confirm appropriate changes in the membrane-free fatty acid composition. Hepatic endothelial cells were isolated by collagenase

perfusion and their purity, as verified with Factor VIII staining, was greater than 90%. Binding assays were performed by adding <sup>51</sup>Cr-labeled tumor cells to TNF-stimulated endothelial cell monolayers and the bound radioactivity was measured by gamma counting. Binding is expressed as a percentage of the total number of radiolabeled cells added ( $\pm$ SEM). Statistical analyses were done using a paired Student *t*-test ( $P < 0.05$ ).

	% Endo binding
1. CX-1 on HSE ( $\phi$ TNF)	18.15 $\pm$ 9.2
2. CX-1 on HSE (TNF)	36.70 $\pm$ 4.3
3. CX-1 (N-3) on HSE (TNF)	11.05 $\pm$ 2.8*
4. CX-1 (N-6) on HSE (TNF)	12.86 $\pm$ 2.1

\* $P < 0.05$  as compared to 2.

These results demonstrate that membrane-free fatty acid modification alters hepatic endothelial cell binding with the  $\omega$ -3 treatment, producing a statistically significant decrease. These changes may be due to altered expression of sialyl-Lewis-X on the surface of the HCRC cells. This decreased endothelial adhesion may result in decreased liver metastases and may therefore be of potential clinical benefit.

## 18. Treatment of Liver Metastasis From Colorectal Cancer by Electrochemotherapy

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**Background and Objectives:** Exposure of tumors to pulses of electricity during chemotherapy enhances membrane permeability and thus intracellular drug delivery. This method, termed electrochemotherapy (ECT), has been shown to produce responses in up to 80% of tumors (melanoma, sarcoma, mammary tumors, pancreatic tumors) transplanted in animal models. We describe the results of intralésional bleomycin-mediated ECT in rats bearing liver metastasis of colon adenocarcinoma.

**Methods:** Thirty-six syngeneic male BDIX rats were used. After laparotomy,  $1.5 \times 10^6$  DHDK 12/Prob colon cancer cells were injected under the liver capsule. Twelve days later, all rats presented a single metastasis. They were randomized into the following groups: B-E- control group; B+E-; B-E+; B+E+; ECT intratumoral injection of bleomycin group; B-E+: application of electric pulses on the tumor group B+E+: ECT (intratumoral bleomycin and 3 min later, application of electric pulses). Twenty-two days later, all rats were sacrificed and the response evaluated.

**Results:** Group B-E- showed no response; group B+E-, one partial response; group B-E+, no response; group B+E+, seven partial responses and two complete responses. The difference of response rate between group B+E+ and the other groups was significant ( $P < 0.05$ ). The mean tumor volume in group B-E- was  $50.6 \pm 34.6$ . The mean tumor volume in group B+E- was  $58.7 \pm 34$ . The mean tumor volume in group B-E+ was  $46 \pm 35.2$ . The mean tumor volume in group B+E+ was  $5.05 \pm 5.7$ . The difference between group B+E+ and the other groups was highly significant ( $P < 0.05$ ).

**Conclusions:** This study demonstrated the efficiency of ECT in the treatment of liver metastasis of colon cancer. If these results are confirmed, it would be possible to test this method in patients with nonresectable colorectal liver metastasis.



## 19. Results of Surgical Treatment on 1,000 Colorectal Cancer Patients: Influence of Age

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**Background and Objectives:** The relationship between results of colorectal resection and age of patients in our experience, as far as postoperative mortality and long-term survival are concerned, was reviewed. The purpose of this retrospective survey was to identify preoperative factors associated with mortality and to define criteria useful in predicting surgical risk in the elderly patients.

**Methods:** We studied 1,000 consecutive patients who underwent surgery for colorectal cancer in our department. Patients were divided into two groups: group 1 included 515 patients over 70 years of age; group 2 comprised 485 patients younger than 70. The data collected included sex, mode of presentation of the patients, the location and Dukes classification of the tumor, the frequency of radical operations, ASA classifications, and the causes of death and 30-day hospital mortality, and the 5-year survival rates of the two groups.

**Results:** Two hundred ninety-four patients in group 1 (57%) and 332 in group 2 (69%) underwent curative resection. In group 1, 139 patients (27%) were admitted as emergencies, compared with only 61 patients (13%) in group 2. The total perioperative mortality rates for the elderly and young group were 12% and 2.9%, respectively. The surgical mortality rates after elective operation in groups 1 and 2 were 8% and 1.7%, respectively, and were not statistically significantly different. Emergency surgery was associated with a significantly higher occurrence of perioperative deaths at any age (23% vs. 11.5%) ( $P < 0.01$ ). The crude actuarial 5-year survival rate after curative resection for group 1 was significantly lower than that of patients aged less than 70 (40% and 60%, respectively,  $P < 0.001$ ). This difference appears to be attributable to an increased mortality from other causes in the elderly. When deaths not caused by colorectal cancer were deleted from the analysis, the probability of survival was the same in both groups, because the perioperative mortality and the long-term prognosis is not significantly different from that of younger patients.

**Conclusions:** Because there is a higher mortality associated with emergency surgery in geriatric patients, a more conservative approach in elective-surgery elderly patients with colorectal cancer can be treated by standard resection.

## 20. PDT of Barrett Esophagus: Kinetics, Localization and Mechanism of 5-Aminolevulinic Acid-Induced Porphyrin Accumulation in the Rat Esophagus

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**Background and Objectives:** Barrett epithelium is a premalignant lesion, with a 40-fold increased risk of developing adenocarcinoma in the esophagus. Photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA)-induced photosensitization may be used to selectively eliminate Barrett epithelium. To find optimal treatment parameters, the kinetics, localization, and mechanism of ALA-induced Protoporphyrin IX (PpIX) accumulation in rat esophagus were studied.

**Methods:** Forty-eight rats, 18 weeks after an esophagojejunostomy, and 48 unoperated rats, received 200 mg/kg ALA i.v. or p.o. At  $t = 0, 1, 2, 3, 4, 6, 12$ , and 24 hr after ALA administration,

porphyrin concentrations in the esophagus were measured using confocal laser scan microscopy (CLSM) and a quantitative chemical extraction method. In the esophageal wall of 20 rats, two enzymes of the haem synthetic pathway—porphobilinogen deaminase (PBGD) and ferrochelatase—and iron concentration were determined.

**Results:** Using CLSM, strong homogenous fluorescence of the basal cell layer of the squamous epithelium lining the normal rat esophagus was shown, whereas fluorescence of the submucosa and muscularis was at background levels. In rats with Barrett esophagus, fluorescence of the Barrett epithelium was more heterogeneous and also restricted to the mucosal layer. No selectivity of PpIX accumulation of Barrett epithelium in favor of squamous epithelium was detected. With the chemical extraction method, porphyrin accumulation in mucosa was 3.4-fold higher than in the muscularis, with a maximum at 3 hr after ALA administration. Results of the i.v. and p.o. groups were similar. Results of the CLSM and chemical extraction methods were comparable. Enzyme measurements showed a higher activity of PBGD in the mucosa compared to the muscularis ( $P < 0.0001$ ). No difference in ferrochelatase activity was found between the two layers of the esophageal wall. Iron concentration in the esophageal mucosa was lower than in the muscularis ( $P < 0.001$ ).

**Conclusions:** In the rat esophagus, ALA-induced endogenous production of PpIX selectively occurs in the mucosa. A possible explanation is a higher ratio of PBGD:ferrochelatase in the mucosa and a relative low iron concentration. This makes ALA most suitable for PDT treatment of Barrett esophagus.

## 21. Neoadjuvant Radiochemotherapy in the Surgical Treatment of Rectal Cancer

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These are the preliminary results of a prospective phase II study in which preoperative radiochemotherapy is integrated in the multidisciplinary management of rectal cancer in order to decrease the rate of local recurrence and to improve the disease-free 5-year survival rates. From April 1995 to June 1997, 18 patients with clinical stage II, III, or IV rectal cancer have been treated with preoperative radiotherapy (54 Gy) and three cycles of leucovorin (25 mg/m<sup>2</sup>/d) and 5-fluorouracil (450 mg/m<sup>2</sup>/d). Pretreatment evaluation included endoscopy, transrectal ultrasound, and CT, among others. Chemotherapy and radiotherapy began concurrently on day 1. Eight to 10 weeks after the onset of neoadjuvant therapy the surgical resections were performed. Two weeks after discharge from the surgical department three additional courses of leucovorin and 5-FU were administered to the patients. The preoperative radiochemotherapy was well tolerated by all patients. Four abdominoperineal resections, 13 low anterior resections, and 1 proctocolectomy were done. There was one case with anastomotic leakage (5.6%) and one case with recurrent abscesses within the small pelvis. The resectability rate with negative margins was 100%. Pathological complete response was seen in three patients (16.7%). The evaluation of the other patients showed stage I in 22.2%, stage II in 38.9%, and stage III in 22.2%. The pretreatment evaluation, however, had shown stage II in 27.8%, stage III in 61.1%, and stage IV in 5.6%. There has been no case of recurrent disease or dying from disease until now. In summary, preoperative radiochemotherapy leads to significant downstaging of rectal carcinoma. An improvement of survival rates and the decrease of the risk of local recurrence are expected. Previous data are encouraging.

## 22. Peritoneal Trauma Stimulates Locoregional and Systemic Growth of Colorectal Carcinoma

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**Background and Objectives:** Following intentionally curative resection of colorectal carcinoma, the most common site for recurrence is locoregional. The mesothelial cell lining of the peritoneum is a major site for tumor cell adherence and growth. Abrasion or arousal of this layer by surgical manipulation may facilitate the adhesion of spilled tumor cells. We demonstrated earlier that peritoneal trauma induces a cascade of events leading to increased adhesion formation. The current study was performed to investigate whether the same mechanism might apply for the adhesion and growth of intraperitoneal (ip) tumor cells.

**Methods:** A reproducible rat model was used in which varying degrees of peritoneal damage (no-touch; mild; severe) were inflicted by standardized rubbing of both uterus horns of WAG rats using gauzes of different texture. Immediately after abrasion of the mesothelial layer,  $0.5 \times 10^6$  syngeneic colon adenocarcinoma cells were injected ip and the abdomen was closed. After 3 weeks tumor growth was assessed semiquantitatively (scores 1–5,  $n = 10$ ) at different ip sites.

**Results:** A significant correlation between the degree of peritoneal trauma and tumor growth at abraded peritoneal surfaces was found (no-touch: median score 0; mild abrasion: score 2; severe: score 4.5). Interestingly, also at nontraumatized sites, the same gradient in tumor growth was present, indicating that local trauma has an impact on the whole organism. This was confirmed by experiments in which the colon tumor was implanted under the renal capsule. Trauma at the site of the uterus was paralleled by enhanced tumor growth at this ectopic site (mean subrenal tumor weight for no-touch: 18 mg; mild trauma: 28 mg; severe: 34 mg). Finally, we found that the tumor enhancing effect of ip trauma could be passively transferred to naive rats with peritoneal washouts, notably with the lymphoid cell fraction (>90% granulocytes).

**Conclusions:** Surgical trauma not only is an important factor in promoting local tumor recurrence but also induces a generalized permissive state for tumor growth.

## 23. Immunohistochemical Investigations of p53, mdm-2, WAF-1, and bcl-2 in Ulcerative Colitis-Associated Carcinomas

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**Background and Objectives:** Long-standing ulcerative colitis (UC) is well recognized as a predisposing condition for the development of colorectal adenocarcinoma (CAC). The role of the tumor suppressor gene p53 and the protooncogenes mdm-2, WAF-1, and bcl-2 both in the development and prognostic outcome of (sporadic) colorectal carcinoma has been extensively investigated in recent years. However, only little is known about the role of those gene products in the development of ulcerative colitis-associated colorectal carcinoma.

**Methods:** Routinely processed tissues from 14 patients with CAC, 5 patients with high-grade dysplasia (HGD), and 5 patients with low-grade dysplasia (LGD) as well as 15 patients with UC but without CAC were immunohistochemically investigated with an-

tibodies against p53 (DO7 and CM-1), mdm-2, WAF-1, and bcl-2. All patients had a history of UC for more than 10 years.

**Results:** Immunohistochemical demonstration of p53 (more than 20% positive tumor cell nuclei) was found in 8/14 (DO7) and 10/14 (CM-1) of CAC, in 2/5 of HGD, 0/5 of LGD, and 1/15 of UC without CAC. mdm-2 immunoreactivity was present in 2/14 CAC, 2/5 HGD, 0/5 LGD, and 1/15 UC cases; one case of CAC showed a pronounced coexpression of p53 (both antibodies tested) and mdm-2. WAF-1 was found in 10/14 of CAC, 4/5 of HGD, 3/5 of LGD, and 11/15 of UC without CAC. WAF-1 was mainly localized in luminal portions of tumors but was never found in invasive areas. bcl-2 overexpression (>20% of tumor cells) was found in 1/14 of CAC, 2/5 both in HGD and LGD, as well as in 1/15 UC cases.

**Conclusions:** Overall, our results are in accordance with findings on sporadic CAC, indicating that UC-associated CAC is developing along the same line as sporadic CAC at least with regard to p53, mdm-2, WAF-1, and bcl-2. Further research may prove whether tumor suppressor genes or oncogenes may be of clinical usefulness both in the diagnosis and prognosis of UC-associated CAC.

## 24. Combined Chemoradiation and Interstitial Ir-192 Implant for T3 and Anal Cancer

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**Background and Objectives:** We have previously shown that 30 Gy + 5-FU + Mitomycin-C (MMC) combined modality therapy (CM) will control T1 and T2 anal cancers with no late morbidity. However, control of T3 and T4 cancers was poor, with an overall local control rate (LCR) of 38%. We now report our experience with the addition of an interstitial Ir-192 single plane implant (SPI) for patients with locally advanced squamous cell carcinoma of the anal canal.

**Methods:** Twenty-one patients were prospectively treated with 30 Gy of external beam radiation therapy (EBRT) + infusional 5-FU (1,000 mg/m<sup>2</sup>) + 1 dose of MMC (10 mg/m<sup>2</sup>). This was followed by a single plane circular implant using a proprietary template that can be loaded with up to eight needles. Median was 29.40 Gy (range, 20–31.60 Gy), delivered at a median rate of 0.44 Gy/hr (range, 0.23–0.56 Gy). All patients were followed at regular intervals with examination and sigmoidoscopy.

**Results:** Twenty-one patients were treated with CM and SPI. There were 13 female and 8 male patients. Nineteen tumors were stage T3, 1 was T4, and 1 was T1 (persistent disease after CM); 18 were N0, 1 was N1, and 2 were N2; 18 out of 21 (86%) were grade 2 or 3. Median tumor size was 6 cm (range, 2–10 cm). The median interval from EBRT to SPI was 5 weeks. The median decrease in tumor size after CM but before SPI was 29% (range, 0%–88%). The LCR after CM + SPI is 86% (18/21). Thirteen of these patients (72%) are NED, three are alive with distant disease (lung and liver), and two died of intercurrent disease. Three patients had persistent disease and underwent abdominoperineal resections (APRs), one was salvaged and two subsequently died of distant disease. The mean follow-up is 21.5 months (range, 3–48 months). The actuarial projected 3-year local control and survival rates are 72% and 61%, respectively. The colostomy-free survival is 81% (17/21). CM and SPI complications included proctitis (three patients) and a nonhealing ulcer (one patient); this patient required an APR. There were no perineal wound dehiscences in patients who underwent APR.

**Conclusions:** Our data indicate that the addition of SPI to our standard CM protocol markedly improves the LCR for this group of anal cancer patients (from 38% to 86%). The sphincter preservation rate is 81% (17/21). CM and SPI were well tolerated with minimal morbidity. Salvage APR was effective in achieving local control.



## 25. Interim Analysis of a Randomized Clinical Trial of Adjuvant Postoperative RT Versus Postoperative RT Plus 5-FU and Levamisole in Patients With TNM Stage II–III Resectable Rectal Cancer

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**Background and Objectives:** In 1992, a randomized clinical trial was started by the PAR Cooperative Study Group with the aim of assessing the effectiveness and toxicity of adjuvant postoperative RT vs. combined RT and CT (5-FU plus Levamisole) in patients with TNM stage II–III resectable rectal cancer (pT3-4, pN0, M0; pT1-4, pN1-3, M0). Primary end point was overall survival; secondary end points were disease-free survival, rate of locoregional recurrence, and treatment-related toxicity/morbidity.

**Methods:** To date, 189 patients (93 males, 96 females; age range, 28–75; median, 65 years) with 0–2 (ECOG) PS were enrolled. Patients were enrolled within 40 days after surgery in a multicenter clinical trial with two arms: arm I, postoperative RT; arm II, postoperative RT and CT (5-FU plus Levamisole), stratified by participating institutions. Beginning within 42 days after surgery, patients randomized in arm I underwent RT (50 Gy) in daily fractions of 2 Gy, 5 days/week for 5 weeks, to tumor bed and locoregional lymph nodes (internal iliac and presacral nodes) with four portals (LL and AP). Patients randomized in arm II began with the first cycle of 5-FU (450 mg/m<sup>2</sup>/d iv bolus on day 1 through 5) plus Levamisole (150 mg/d orally on day 1 through 3). Postoperative RT was delivered in the next week at the same dosage and schedule as in arm I. The other five cycles of CT (5-FU every 28 days, and Levamisole every 15 days for the whole length of 5-FU administration) continued at the end of RT.

**Results:** Patients in both groups (arm I: n = 93; arm II: n = 96) showed no significant difference as regards sex, age, PS, type of operation (sphincter saving resection or abdominoperineal excision of the rectum), pT, pN stage of disease, number of sampled lymph nodes, and grading. On the average, patients began RT 44 and 48 days from surgery (range: 26–106 days) in arm I and arm II, respectively; CT was started 39 days from surgery in arm II. To date, 25 and 33 relapses have been observed in arms I and II, respectively; 15 patients died both in arms I and II. As regards toxicity, radiodermatitis (6%, grade III), diarrhea (5%, grade III), and cystitis (2%, grade III) were observed in arm I while radiodermatitis (8%, grade III), diarrhea (11%, grade III; 3%, grade IV), and leukopenia (3%, grade III; 3% grade IV) occurred in arm II. These preliminary findings suggest that further information should be obtained from clinical trials with regard to the role and type of adjuvant treatment in resectable rectal cancer, as a similar effectiveness coupled with less morbidity can at present be related to postoperative RT alone compared to postoperative RT and CT.

## 26. Surgical Treatment of Lung Metastases: Prognostic Factors for Long-Term Survival (PFS)

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Surgical resection of lung metastases is an established therapy for a large number of primary tumors, but there is some controversy about PFS. We performed a retrospective review of a series of 85 patients (100 operations) that have been operated for resection of lung metastases in our department from 1968 to 1996. The Kaplan-Meier product limit method was used to estimate the probabilities of overall survival after surgery, the log rank test for the univariate analysis of PFS, and the Cox proportional-hazards model in the subsequent multivariate analysis. The primary tumor was a soft tissue sarcoma in 18 patients, a bone tumor in 13, a head and neck tumor in 12, breast carcinoma in 10, colorectal cancer in 7, and miscellaneous tumors in 25 patients. These patients underwent 81 atypical resections, 3 segmentectomies, 48 lobectomies, 11 bilo-

bectomies, and 3 pneumonectomies. The operative mortality was 4% and the morbidity 19%. Fifty-three patients had surgery as the only treatment for their metastases. The mean follow-up after resection was 22.13 months (1–146). Seven patients (8.2%) have been lost to follow-up. The actuarial 5-year survival rate was 29.2%. By univariate analysis, the following factors were associated with prognosis after resection of lung metastases: location and histology of the primary tumor, duplication time of the metastases, greatest dimension of the largest metastases (greater vs. less than 4 cm), radicality of the resection, involvement of the resection margins, and use of adjuvant therapy ( $P < 0.05$ ). The stage of the primary tumor, synchronous vs. methachronous diagnosis of the metastases, unilateral vs. bilateral metastases, the number of metastases resected, the type of lung resection, the presence of mediastinal lymph node metastases, and the number of operations each patient had undergone were not found to be significant prognostic factors. After multivariate analysis, only the dimension of the metastases and involvement of surgical margins have been found to be independently associated with survival after lung resection for metastases. Surgical excision is a safe and effective therapy for lung metastases from a large number of primary tumors, provided a complete resection is feasible.

## 27. Angiogenesis, Expression of p53, c-erbB-2, and Clinicopathological Features in Male Breast Cancer

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**Background and Objectives:** Angiogenesis and overexpression of p53 and c-erbB-2 have been shown to correlate with tumor aggressiveness and patient survival in female breast cancer. Limited data exist on coexpression of these markers in male breast cancer.

**Methods:** In the present study clinicopathological correlation of tumor microvascular density (MVD), immunoreactivity of p53 and c-erbB-2 with tumor stage, grade, estrogen, and progesterons receptor (ER and PR) status and survival was done on 17 male breast cancers. Angiogenesis and overexpression of p53 and c-erbB-2 were detected on archive paraffin-embedded material, following staining with specific anti-CD34, anti-p53, and anti-c-erbB-2 antibodies. Vascularity was defined as a mean MVD under  $\times 200$  magnification.

**Results:** Median age of the patients was 64 years (range, 41–90) and median follow-up was 4.5 years (range, 1–9 years). Eight patients had T3-4 lesions. Four patients had nodal metastases. In four patients, axillary clearance was not done. None of the patients had distant metastases at the time of disease presentation. Five patients died of metastatic disease and three patients died of unrelated causes. One patient had recurrent disease and the rest were free of disease. Positive p53 nuclear staining was found in 6/17 patients; all patients but one had high-grade tumors. Positive c-erbB-2 staining was found in 9/17 tumors. MVD was higher in high-grade tumors than in low-grade tumors (mean  $\pm$  SD MVD:  $115 \pm 9$ ,  $120 \pm 121$ , and  $136 \pm 80$  for low-, intermediate-, and high-grade tumors, respectively), in more advanced stage (stages I and II  $101 \pm 41$  vs. stages III  $147 \pm 77$ ) and more advanced T-stage (MVD:  $99 \pm 31$  for T1-2 vs.  $136.7 \pm 70$  for T3-4 tumors). A weak positive correlation was found between MVD and patient survival (MVD:  $123 \pm 29$  for patients who died of disease vs.  $105 \pm 54$  for survivors). No correlation between positive immunoreactivity for p53 and c-erbB-2 and ER and PR status, disease stage, or survival was found.

**Conclusions:** Microvessel density was higher in more aggressive tumors as expressed by larger tumor size, higher grade, and more advanced disease stage. Positive p53 immunoreactivity correlated with high-grade tumors.

## 28. Aesthetic Results of the Breast Cancer Conservative Treatment in the Lower Quadrants

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The quality of the cosmetic outcome of breast cancer conservative treatment is strictly related to the primary location of the tumor. It is widely accepted that the lower quadrants can leave more residual deformities than the others. In order to prevent these poor results, a new surgical approach has been adopted: a wide lumpectomy associated with a superior pedicle mammoplasty (with postoperative irradiation) was the treatment of choice in the last 25 cases of lower quadrants tumors. In the last five years (1992–1997) at the Surgical Clinic I of the University of Florence, 1,299 cases of breast cancer have been treated: 966 with conservative procedures and 220 located in the lower quadrants (127 central, 51 outer, 42 inner). A case control study (with a ratio 2:1) has been settled comparing cosmetic results in patients with or without mammoplasty. The patients were matched by age, size of the tumors, location (central, inner, outer), and adjuvant treatments. The results demonstrate that there is a significant improvement of the cosmetic outcomes with this type of reconstruction. The authors also argue the indication to a mono- or bilateral mammoplasty, concerning the discrepancy between the level of the inframammary crease and the breast size. The poor cosmetic results of the treatment of tumors of the lower quadrants can be avoided by employing a remodeling mammoplasty that, through a redistribution of the residual breast volume, can preserve a normal-appearing breast.

## 29. Are Breast Complaints Really Related to Breast Cancer? Results From a Retrospective Study in 2,561 Symptomatic Patients Observed During a 14-Year Period

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**Background and Objectives:** Breast complaints are especially related to the age of the patients and their menopausal status, but a reliable connection with breast diseases was not proved. In our retrospective study we tried to define a correlation between risk of breast cancer, fibrocystic breast disease (FBD), and breast complaints.

**Methods:** A review of 2,561 consecutive self-selected symptomatic new patients observed during a 14-year period is reported. Each patient was asked to relate one or two chief complaints as follows: breast pain, breast lump(s), and nipple discharge. Only 449 patients (17.5%) had already breast ultrasonography or mammography. Three age groups of patients were sorted out: group A (40 years old or younger) = 45.9%, group B (41–55 years) = 27.8%, and group C (over 55 years) = 26.3%.

**Results:** Patients' reported symptoms (breast lump or pain, nipple discharge) and signs at clinical examination are showed below.

Group	Lump	Pain	Nipple discharge	Mass	Nodularity	Nipple Discharge	No signs
A	36.8%	61.0%	2.2%	53.7%	38.6%	4.3%	3.4%
B	51.4%	45.8%	2.8%	46.9%	43.1%	9.1%	1.8%
C	87.8%	9.1%	3.0%	52.1%	26.3%	5.8%	1.3%
All patients	89.0%	70.8%	4.2%	51.4%	36.6%	6.0%	2.4%

Pain was most common in group A patients ( $P < 0.01$ ) and lump in group C and B patients ( $P < 0.01$ ). In 87.9% of the examined patients, a breast mass or nodularity was found. Two hundred seventy-one (10.5%) patients (0.9%, 12.1%, and 25.8% in groups A, B, and C, respectively) underwent surgery for breast cancer. Although FBD was the more frequent finding in all groups, the onset of cancer in 556 patients with FNAB-confirmed FBD over a median follow-up of 57 months (range, 15–156) was similar to that reported for the general population. Only in group C was a statistically significant correlation between malignancy and breast lump evident ( $P < 0.01$ ), but no correlation between cancer and breast pain was found in any group.

**Conclusions:** Only 10% of the symptomatic patients may have cancer and a reliable correlation between breast complaints and risk of cancer does not seem to exist. Therefore, further imaging work-up is warranted only in a minority of symptomatic patients.

## 30. Using Sappey Anatomy for Identifying Sentinel Lymph Nodes in Breast Cancer

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The most important prognostic factor of breast cancer is an adequate staging of the axillary lymph nodes, which influences both adjuvant and surgical therapy. Morton has successfully adapted the method that he had originally developed for identifying "sentinel" lymph nodes in melanomas to the purposes of examining axillary lymph nodes in patients with breast cancer. Using this procedure he has also made staging simpler and more accurate. Due to the close relationship between the plexus areolaris, the plexus subareolaris, and the plexus periareolaris, the special lymphatic system of the breast makes it possible for the vital stain to be injected under the skin of the areola rather than round the tumor itself. The axillary lymph drainage of 85 randomly selected patients with breast cancer was studied. Of these 85 patients, 55 underwent direct breast lymphography. For visualizing lymph vessels, Patent Blue was injected intracutaneously into the area of the areola. The lymph vessels and lymph nodes outlined on radiographic pictures after Lipiodol Ultrafluid was injected into a prepared collector lymph vessel. The dissection of axillary lymph nodes was started by preparing the lymph nodes that stained blue. The results were evaluated in a 5-year follow-up examination. In 30 patients, sentinel lymph nodes were identified by comparing results yielded by the two methods. Patent Blue was injected intracutaneously into the region of the areola mammae; then, after the exposure of the axilla and the isolation of the blue-colored lymph nodes, Patent Blue was injected around the primary tumor to induce the discoloration of further lymph nodes. Our observations suggest that the procedure when the vital stain is injected into the plexus areolaris located in the region of the areola mammae is far simpler, as identical lymph vessels and lymph nodes get discolored in the axilla. In addition to its role in the identification of the sentinel lymph node, the vital stain injected into the skin of the areola shows lymph node metastasis by visualizing lymphostasis in the form of a pathological outline of the lymph nodes on the skin. The data obtained in the 5-year follow-up suggest that the status of the axillary lymph drainage clearly indicates the likelihood of distant metastases and it can also account for the observation made by Giuliano concerning the increased mortality rate of breast cancer in the first 7 postoperative years.

### 31. Ultrasound Localization of Impalpable Breast Lesions

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Impalpable lesions detected by mammography require accurate location before excision. This study assesses the efficacy of ultrasound-guided location in terms of successful location of lesions and adequate excision. One hundred forty-eight patients with impalpable lesions easily visible on ultrasound underwent ultrasound-guided location biopsies between September 1989 and February 1996. Location was performed using an Aloka SSD 620 with a 7.5-MHz linear array probe. The depth of the lesion and its diameter was recorded. All lesions were successfully located and excised at the initial biopsy procedure. The mean maximum diameter of lesion located at ultrasound was 11 mm (range, 3–30), compared to mean histological size of 13.6 mm (range, 4–33;  $r = 0.76$ ,  $P < 0.001$ ). The mean maximum diameter of tissue removed was 57.5 mm (range, 10–110). Ninety-nine of the 148 ultrasound-located biopsies (67%) were malignant. Excision was complete in 87 (88%) of the malignant cases. Five patients had further excisions and seven underwent mastectomy. The proportion of women with impalpable breast lesions undergoing ultrasound-guided location has increased from 3% in 1990 to 36% in 1995. Well-defined impalpable lesions can be successfully located using ultrasound. The procedure is simple, convenient, and noninvasive.

### 32. Vaccination of Breast Cancer Patients With Autologous Tumor-Associated Antigens Results in Reduction of Serum Interleukin 6

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Previous studies have shown that Hodgkin and non-Hodgkin lymphoma, multiple myeloma, ovarian carcinoma, renal cell carcinoma, and breast carcinoma patients with high serum concentrations of interleukin 6 (IL-6) have a poorer prognosis than patients with normal serum concentrations of IL-6. Further, the IL-6 concentration in the serum of diffuse large-cell lymphoma and Hodgkin lymphoma patients decreased when patients responded to chemotherapy. We have shown that when 27 breast cancer patients were vaccinated with autologous tumor-associated antigens (aTAA) mixed with the biological adjuvants IL-2 and GM-CSF, there was a significant increase ( $P = 0.034$ , paired  $t$ -test) in the ratio of <sup>3</sup>H-thymidine incorporated into their peripheral blood lymphocyte DNA in response to autologous antigen stimulation (lymphocyte blastogenesis assays) from  $1.46 \pm 0.51$  before vaccination to  $2.20 \pm 1.61$  after vaccination. When we compared serum CA 15-3 concentrations in 18 breast cancer patients before and after vaccination with aTAA, there was a significant decrease ( $P = 0.034$ , paired  $t$ -test) in the serum concentration from  $48 \pm 46$  to  $41 \pm 40$  U/ml. There was no associated change in the serum CEA concentration ( $2.0 \pm 1.9$  ng/ml before vaccination and  $1.9 \pm 1.5$  ng/ml after vaccination;  $P = 0.578$ , paired  $t$ -test) in 17 breast cancer patients. In the present study, IL-6 concentrations were found to be  $51.1 \pm 150.5$  pg/ml in 41 breast cancer patients before vaccination and  $8.76 \pm 6.33$  pg/ml in 27 patients after vaccination. There was a significant decrease ( $P = 0.046$ , chi-square analysis of independence) in the proportion of breast cancer patients with serum IL-6 concentrations greater than 15 pg/ml from 26.8% (11 of 41 patients) prevaccination to 7.4% (2 of 27 patients) postvaccination. The significantly lower serum concentration of IL-6 in the breast cancer patients vaccinated with aTAA is the first associated with any immunotherapy. This suggests that vaccination of breast cancer patients with aTAA not only results in an increase in peripheral blood lymphocyte blastogenic response to aTAA and a decrease in the serum concentration of the breast tumor marker CA 15-3, but may cause a decrease in the serum concentration of the cytokine IL-6.

### 33. Chest Wall Resection in 44 Patients With Recurrent Breast Cancer: Indications and Results

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**Background and Objectives:** The aim of this study was to ana-

lyze the indication for and morbidity from chest wall (CW) resection for recurrent breast cancer in relation to survival.

**Methods:** The clinicopathological and outcome data were recorded from 44 patients who underwent a CW resection for recurrent breast cancer. CW reconstruction consisted of steel wire ( $n = 9$ ) Vycril ( $n = 12$ ) and Marlex ( $n = 20$ ). Soft tissues were closed primarily ( $n = 10$ ), transposition of omentum ( $n = 31$ ), the contralateral breast ( $n = 30$ ), LD-flap ( $n = 2$ ), and with split skin graft ( $n = 28$ ).

**Results:** Mean age at primary diagnosis was 47 years and at CW resection 51 years. Overt distant disease was diagnosed in 27%. Previous therapy consists of mastectomy (all), radio- ( $n = 39$ ), chemo- ( $n = 10$ ), or hormonal therapy ( $n = 4$ ). Complications were seen in 25% (omentum necrosis  $n = 1$ , infection  $n = 7$ , pulmonary  $n = 8$ ). Thirty patients were rendered tumor-free (no distant disease, tumor-free margins): 18 had recurrence; 1 isolated local recurrence, 12 distant recurrence, and 5 combined. The median survival was 8.9 years with an actuarial 5-year survival of 62%. After palliative resection in 14 patients, the median survival was 2.3 years and the 5-year actuarial survival 21%.

**Conclusions:** CW resection for recurrent breast cancer may result in good local control with limited morbidity and a 5-year survival of 63% in completely resected cases and of 21% after palliation. This treatment option should always be considered in women with locally recurrent breast cancer.

### 34. Variation in Breast Reconstruction Rates After Mastectomy for Breast Cancer in a Single-Payer Medical System

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**Background and Objectives:** The aim of the study was to determine the rate of breast reconstruction (BR) after mastectomy for breast cancer and to assess factors that may have influenced the rate in a single-payer medical system.

**Methods:** This is a population-based retrospective cohort study taken in Ontario, Canada, which included all women with breast cancer undergoing mastectomy and/or BR from 1 January 1984 to 31 December 1994. The main outcome measure was the ratio of the number of women undergoing BR after breast cancer to the number undergoing mastectomy for breast cancer.

**Results:** In the time period analyzed, 25,059 women in Ontario underwent mastectomy for breast cancer and 1,568 underwent BR. The rate of mastectomy declined from 58.3 per 100,000 women in 1984 to 42.9 in 1994. The ratio of the number of BR to the number of mastectomies per year did not change; 7.9 BR procedures were performed per 100 mastectomies in 1984, as compared to 7.7 BR procedures per 100 mastectomies in 1994. Regional variation in BR was evaluated for a 2-year time period (1992–1994). The ratio of BR procedures to mastectomy was twice as high for those living in the greater Toronto area (GTA) as for those living in all other regions of Ontario (10 vs. 4.3 BR procedures per 100 mastectomies, respectively). The GTA is a large urban region with a population of three million. The distribution of institutions where BR was performed in 1994 was evaluated. Two institutions in the GTA, one hospital with an academic affiliation and one community hospital, accounted for 60% of the BR procedures performed in Ontario. Both hospitals have surgical teams with an interest in BR. In comparison, no or few (<1%) BR procedures were performed in two other major urban areas with academic medical centers.

**Conclusions:** Over the 10-year time period analyzed, the average rate of BR in a single-payer system was similar to the rate reported for the United States in 1990 (6.2 vs. 7.2, respectively). The number of BR procedures per 100 mastectomies performed did not increase over the 10-year period. Marked regional variation in the performance of BR was found even between academic medical centers. Proximity to a large urban center having institutions with expertise in BR was associated with a twofold higher rate of BR.



### 35. Is Therapeutic Radiation Following Breast Conservation Surgery Always Necessary?

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The controversy concerning the need for adjuvant radiotherapy following wide local excision of infiltrating ductal carcinomas (IDC) continues. Studies show that while adjuvant radiotherapy reduces the incidence of local recurrence, it does not prolong survival. Adjuvant radiotherapy, although well tolerated by most, is not innocuous. Morbidity including breast and chest wall pain, moist desquamation, hyperpigmentation of the irradiated skin, fibrosis and shrinkage of the treated breast, rib fractures, pneumonitis, and sarcomas have been reported with an incidence varying from 1% to 28%. We wondered if a subset of IDC patients could be identified so that treatment with wide local excision alone would sufficiently reduce the risk of local recurrence to acceptable rates. To answer this question, 193 patients with stage I and II IDC treated with wide local excision without adjuvant radiotherapy between 1984 and 1988 were identified and followed prospectively for a median follow-up period of 8 years. We report on 60 patients, of which 43 remain disease-free to date. The local recurrence rate, initially assessed at 16% at 4 years (19% premenopausal and 10% postmenopausal) has increased to 30% at 8 years. We conclude that postmenopausal patients, thought by some investigators to be at lower risk for local recurrence following wide local excision, may in fact not be. For the final presentation we will have analyzed nearly 200 patients' records to identify subgroups that may not benefit from adjuvant radiotherapy.

### 36. Palliative Therapy for Endocrinopathies Resulting From Metastatic Neuroendocrine Tumors

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**Background and Objectives:** Historically, the treatment of endocrinopathies from metastatic neuroendocrine tumors was surgical debulking. With new technology, the ability to provide palliative tumor reduction has increased, allowing more patients with endocrinopathies to be effectively treated. The purpose of this study was to assess retrospectively the efficacy of multimodality treatment for palliative control of endocrinopathies from metastatic neuroendocrine tumors.

**Methods:** A retrospective review was done of 23 endocrinopathies in 20 patients with metastatic neuroendocrine tumors presenting for surgical consultation. All patients but one were interviewed and reviewed in follow-up by one surgeon (J.L.P.). Demographic data, years of follow-up, resolution of endocrinopathy, and tumor/hormonal markers were documented.

**Results:** Twenty patients, four of whom were MEN 1, presented with symptoms related to the production of hormonal factors from metastatic neuroendocrine tumors. One patient had synchronous endocrinopathies, both a recurrence pheochromocytoma and a metastatic islet cell tumor secreting PTHrp. Another MEN 1 patient had endocrinopathies resulting from overproduction of gastrin, ACTH,

and glucagon. The remaining patients presented with a single endocrinopathy (one PTH, three gastrin, three insulin, eight serotonin, two pancreatic polypeptide, one glucagon). Treatment modalities of metastasis consisted of a combination of surgical debulking, cryosurgery, alcohol injections, chemoembolization, systemic chemotherapy, and hormonal manipulation. Five patients had complete resection and are alive without endocrinopathies or residual disease at 14–58 months (mean, 35 months). Nine who have had resolution of their endocrinopathy, however, have known residual disease and remain on hormonal reduction drugs at 1–55 months (mean, 31 months). Three patients had rapid progression and recurrence of their endocrinopathy requiring further multimodality therapy at 18–36 months following initial surgery (mean, 24 months). Three patients had noncytoreductive surgery of their tumors and continue to progress with their endocrinopathy despite chemo/hormonal therapy at 36–42 months (mean, 38 months).

**Conclusions:** Excellent palliation from the endocrinopathy can be achieved with cytoreduction of the tumor and hormonal manipulation. Rapid recurrence and failure to cytoreduce the tumor burden will result in poor control of the endocrinopathy. This experience suggests that cytoreduction should be attempted in all patients with endocrinopathies, since medical management alone provides limited palliation.

### 37. Long-Term Survival in Patients With Complete Resection of Melanoma Metastatic to the Adrenal Gland

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Survival of patients with AJCC stage IV melanoma is poor, although there have been occasional long-term survivors with limited metastases treated by surgical resection. The diagnosis of melanoma metastatic to the adrenal gland, although rare, has been made possible before autopsy with advanced imaging technology. The purpose of this study was to investigate the survival of melanoma patients with adrenal gland metastases who underwent surgical resection. Eighty-three patients with a premortem diagnosis of adrenal metastasis were identified retrospectively from over 8,000 patients registered in our melanoma database and charts were reviewed. Univariate survival analysis was calculated using the log rank test. Median survival for the total group was 9.3 months (1–67 months), and 3-year estimated overall survival was 11%. Twenty-seven patients underwent surgical exploration, of which 18 were rendered NED: 12 by adrenalectomy alone, and 6 by adrenalectomy and synchronous additional metastasectomy. Nine patients underwent palliative resection. Complete resection of all known disease ( $P = 0.012$ ) and those patients resected with asymptomatic adrenal lesions ( $P = 0.03$ ) had a statistically significant improvement in survival. Median survival for the patients rendered NED was 25.7 months, compared to 9.2 months in those patients with residual metastatic disease. The 3-year survival estimate for patients rendered NED by resection was 38%, compared to 3% in patients not explored. In conclusion, patients with asymptomatic melanoma adrenal metastases, including other limited synchronous metastases, appear to have improved survival if completely resected.

### 38. Second Primary Testicular Germ Cell Tumors in Patients With Initial Stage I Disease: Prevalence and Prognosis—A 30-Year Single-Center Experience

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**Background and Objectives:** Development of second testicular tumors is influenced by effects of systemic chemotherapy for the first tumor. Therefore, we studied prevalence of second tumors in patients with initial stage I disease, in which no systemic treatment was given. Because from 1980 all stage I patients entered a surveillance study with an intensive follow-up, we hypothesized that after 1980 second tumors were diagnosed at an earlier stage of disease.

**Methods:** Records of 445 testicular cancer patients with stage I disease treated with retroperitoneal lymph node dissection, radiotherapy, or surveillance between 1967–1997 were reviewed. Bilateral testicular cancer (BTC) in 144 patients (66 nonseminomas, 78 seminomas) treated between 1967–1979 was compared to BTC in 301 patients (197 nonseminomas, 104 seminomas) treated between 1980–1997 with respect to prevalence, interval between first and second tumor, stage of second disease, histology, treatment, and prognosis.

**Results:** The prevalence of bilateral tumors was 5.6% between 1967–1979 and 2.7% between 1980–1997 ( $P < 0.25$ ).

	1967–1979 (n = 144)	1980–1997 (n = 301)	Total (n = 445)
Prevalence in % (n)	5.6 (8)	2.7 (8)	3.6 (16)
Mean interval in years	8.0	4.0	5.9
Survival in % (n)	75 (6/8)	100 (8/8)	87.5 (14/16)

In the period 1967–1979, six patients had stage I disease and two patients had stage III disease at diagnosis of the second tumor. In the period 1980–1997, all patients had stage I second tumors. Four patients in the first and five patients in the second period showed no concordance in histology of both tumors, all other patients had bilateral tumors of the same histologic type. Of the patients treated between 1967–1979, two patients died of disease or toxicity after chemotherapy for stage III second disease. The remaining six patients are alive with no evidence of disease (NED). All BTC patients treated between 1980–1997 are alive with NED.

**Conclusions:** Overall prevalence of BTC in stage I patients is 3.6% and decreased over the past three decades. Intensive follow-up using improved diagnostic procedures has resulted in earlier diagnosis and lower stage of disease, resulting in improved prognosis of second testicular tumors.

### 39. Cytoreductive Surgery and Intraperitoneal Chemotherapy: Hemodynamic Consequences During Intra-Abdominal Irrigations

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**Background and Objectives:** Peritoneal cavity irrigations after cytoreductive surgery may induce intra-abdominal pressure modifications. The aim of this study was to observe the hemodynamic modifications induced by filling and emptying peritoneal cavity during the immediate postoperative period.

**Methods:** This prospective and descriptive study included 11 patients with normal left ventricular function (ejection fraction >50%). All the patients

undergoing cytoreductive surgery and intraperitoneal chemotherapy have a standardized monitoring (pulmonary artery catheter with continuous cardiac output) and standardized anesthesia protocol during the preoperative and immediate postoperative period. Swan Ganz catheter was used for continuous cardiac index monitoring (CI; L/m<sup>2</sup>) and for intermittent measurement of pulmonary capillary wedge pressure (PCWP; mm Hg). The abdominal irrigation catheter allowed for continuous measurement of intra-abdominal pressure (AbP; mm Hg). The hemodynamic data were collected before surgery (T0). During peritoneal cavity irrigations after surgery, CI, PCWP, and AbP were noted at several times, after abdominal cavity closing (T1) and after the first abdominal cavity filling (T2). A last series of measurement was performed in the intensive care unit (patient being deeply sedated and under artificial ventilation): before last but one abdominal cavity emptying (T3), and before and after last one abdominal cavity filling (T4 and T5). For statistical analysis, a Friedman two-way Anova test (Fried T) and a Wilcoxon test (Wilc T) were used to study the significance of intra-abdominal pressure and hemodynamic parameter modifications (statistical significance:  $P < 0.05^*$ ).

**Result:** Results are as follows:

Fried T	T0	T1	T2	T3	T4	T5	P
AbP		11.3 ± 7.2	19.4 ± 8.2	6.6 ± 4.1	1.1 ± 4.6	8.4 ± 4.7	0.000*
PCWP	11.6 ± 5.5	10.3 ± 4.6	11.8 ± 4.1	8.0 ± 4.6	6.3 ± 4.1	8.3 ± 4.0	0.024*
CI	3.5 ± 0.78	4.1 ± 0.75	3.4 ± 0.52	4.0 ± 0.9	4.0 ± 0.9	4.2 ± 0.9	0.153
Wilc T		T2 > T1		T3 > T4		T5 < T4	
AbP		0.033*		0.033*		0.033*	
PCWP		0.025*		0.068		0.038*	

**Conclusions:** Peritoneal cavity filling and emptying induce not only intra-abdominal pressure modifications, but also cardiac preload variations. However, in patients with normal cardiac status, there is no effect on cardiac output.

### 40. Pelvic Exenterations for Gynecological Malignancies

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One hundred forty-one patients underwent pelvic exenteration between January 1980 and March 1997 in the Department of Surgery of the Institut Paoli-Calmettes: 54 anterior, 38 total (30 suslevatory exenterations), 37 posterior (24 suslevatory exenterations), 12 atypical procedures. The mean age was 53 ± 12 (range, 26–81). One hundred and one exenterations were done for carcinoma of the cervix (72%). Forty were done for other malignancies: endometrium, 14; ovarian carcinoma, 14; vagina, 4; sarcoma, 3; vulva, 2; fallopian tube, 2; mulleroblastoma, 1. There were 60 primary exenterations and 81 secondary exenterations for recurrence. The resection was considered retrospectively (i.e., histological findings) to be curative in 75 cases [37 primary exenterations (49%) and 38 secondary exenterations (51%)] and palliative in 66 cases [23 primary exenterations (35%) and 43 secondary exenterations (65%)]. Fifty-eight low colorectal anastomosis were performed among 75 posterior and total exenterations (77%): in 23 of 37 posterior (62%) and 29 of 38 total exenterations (76%). Colorectal anastomosis was performed by hand suture in 11 patients and by end-to-end stapling in 47 patients. A protective transverse colostomy was fashioned in 29 patients. An urinary derivation was made in 94 cases: 15 bilateral cutaneous ureterostomies before 1984, 56 transintestinal ureterostomies, 23 modified Indiana pouch performed by continent urinary diversion. Reconstructive procedures included 27 epiploplasties and 19 vaginal pelvic feeling using rectus abdominus myocutaneous flap. The hospital mortality was 8.5% (12/141). The morbidity was 50% (70/141). The overall actuarial survival was, for all patients, 45%, 36%, and 30% at 2, 3, and 5 years; for the curative group (n = 75), 67%, 58%, and 48% at 2, 3, and 5 years; for the palliative group (n = 66), 19%, 4%, and 4% at 2, 3, and 5 years ( $P < 0.0001$ ). Curative resection was the first predictive factor for long-term survival: 2, 3, and 5 years actuarial survival was, respectively, 75%, 69%, and 61% in the group of primary exenteration (n = 37) and 61%, 48%, and 37% in the group of pelvic exenteration for recurrence.

#### 41. Calcemia and Parathyroid Hormone in Patients Undergoing Thyroidectomy

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Prevention of postoperative complications is due to a correct surgical technique preserving parathyroid glands. In this prospective study we analyzed correlation between pre- and postoperative calcemia and parathyroid hormone (PTH) in all patients submitted to thyroidectomy. From January to December 1996, 213 patients were submitted in our institution to a unilateral or bilateral thyroidectomy both for benign or malignant pathology. There were 180 (84.5%) females and 33 (15.5%) males, with an average age of 44.5 (range, 15–74). One hundred fifty-six (73.2%) patients were submitted to a total or near total thyroidectomy and 57 (26.8%) to a unilobar thyroid resection. The disease in the resected thyroid gland included benign disease in 175 (82.2%) and malignant neoplasm in 38 (17.8%). All patients were prospectively tested for preoperative and postoperative evaluation of calcemia and PTH media molecula levels, at day 1 and 3, respectively. All patients with one or plus value not recorded were excluded from statistical evaluation. The parathyroid glands were preserved whenever possible and if at the end of intervention ischemic aspect or accidental exeresis of parathyroid gland were noted, the auto-transplantation into a pocket of the sternocleidomastoid muscle was done. This event occurred in five (2.3%) cases. Transient postoperative hypocalcemia occurred in 26 (12.2%), all in the group of bilateral thyroid resection. Six (2.8%) patients with serum calcemia under 8.1 mg/dl did not reveal any symptom, while in two (0.9%) normocalcemic cases a transient acral numbness and paresthesias were found. Only eight (3.8%) patients developed a permanent hypoparathyroidism. From the analysis of preliminary data on 40 patients, no correlation (calculated through Spearman coefficient) was observed between calcium and PTH circulating levels on the first and third day. The analysis referred to those patients with symptomatic hypocalcemia showed a better correlation between decreased serum calcium and PTH. In fact, among 14 (6.6%) patients in which serum calcium decreased under 8.1 mg/dl, only 9 (4.2%) also presented a decreased PTH value. While in the others, this correlation was not evident. In this study, PTH was confirmed to be not a prognostic factor predicting permanent hypoparathyroidism. Our study revealed precece hypoparathyroidism as uncommon sequela of thyroid surgery, especially when an accurate identification of parathyroid glands is performed, but no correlation was observed between calcium and PTH postoperatively.

#### 42. Surgery for Metastatic Spinal Tumors

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Spinal marrow compression is often a primary clinical sign of metastatic involvement of the spine and if it is detected early, surgery may prevent further aggravation and in some cases may correct neurological disorders. The purpose of this study was to evaluate efficacy of surgery in patients with metastatic tumors of the spine as a component of complex treatment for cancer. Since 1995, we have performed surgery in 12 patients with metastatic involvement of the spine. Distribution of tumors by morphology was as follows: metastasis of breast cancer (7), metastasis of ma-

lignant hemangiopericytoma (1), metastasis of osteogenic sarcoma (1), metastasis of hypernephroma (2), metastasis of prostate cancer (1). Distribution of cases with respect to tumor site in the spine was as follows: cervical spine (5), thoracic spine (4), lumbar spine (3). Preoperatively, all the patients had neurological symptoms, including superior indolent and inferior spastic paraparesis (3), inferior indolent paraparesis (3), inferior spastic paraparesis (1), and inferior spastic paraplegia (3). The five patients with metastatic tumors of the cervical spine all underwent resection of vertebral bodies with defect correction and stabilization with porous carbon implants (carbon syntactic foam, CSF). The patients with metastatic tumors of the thoracic and lumbar spines underwent palliative posterior decompression laminectomy due to advanced disease (fixation with Hartington pins in one case). Postoperatively, all the patients presented with analgesic effect; regression of neurologic symptoms was observed in seven cases, including one patient with inferior spastic paraplegia (who now walks without support). The patients' postoperative course was uneventful. Postoperative radiotherapy as a component of complex treatment was given to 2 patients; chemotherapy was performed in all 12 patients. Of the 12 patients, 2 died from disease progression at 3 months following surgery; the remaining patients are alive, with no evidence of disease progression (follow-up ranging from 3 to 16 months). Spinal surgery makes a significant contribution to treatment and considerably improves quality of life of patients with metastatic spinal involvement.

#### 43. Fibromatosis: A Prospective Cohort Study for Local Control

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**Background and Objectives:** Fibromatosis is a horrendous problem and its rarity prevents a consistent treatment approach. Our population-based experience, mostly in recurrent desmoids, in all sites, including the pelvic area, over the last 10 years has been analyzed to provide a framework for dealing with this disease.

**Methods:** A total of 13 patients have been managed on a treatment protocol of preoperative Adriamycin (30 mg continuous infusion  $\times$  3 days) and radiotherapy (10  $\times$  300 cGy), followed by surgery. Three patients have been managed with observation and/or tamoxifen. The mean age of these patients is 28 years (range, 18–40). Four lesions were found in the arm and shoulder, three in the leg, and six in the trunk, of which three involved the pelvic region. Failures of previous procedures in the protocol patients was 1.5, with a range of 0–3 per patient.

**Results:** Clear margins were obtained in eight of the patients, all of whom were controlled at a mean follow-up of 46 months, with a range of 12–90 months. One patient recurred outside the treatment area for a failure rate of 15%. Two patients with positive margins after protocol developed recurrent but stable disease in the leg and one is currently free of disease at 6 months. Three patients who were observed have arrest of their disease; two in the pelvic area, one with tamoxifen and one without; and one in the paravertebral area. Symptoms of these tumors in these patients are relatively minimal.

**Conclusions:** For potentially resectable lesions, this protocol provided unprecedented local control even after failing multiple surgeries. Amputation, pelvic exenteration, or other ablative surgery is not justified to obtain clear margins, as this disease can frequently be managed by hormonal manipulation and may arrest without long-term morbidity.



#### 44. Isolated Limb Perfusion (ILP) With Tumor Necrosis Factor (TNF) and Melphalan for Multifocal Soft Tissue Sarcoma (STS): Limb Salvage in Fatal Disease

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The prognosis of limb multifocal soft tissue sarcoma (STS) is dismal and local control is a special problem. Even when resection is feasible, recurrence is the rule. ILP with TNF and melphalan has recently been shown to be effective in STS. The purpose of the present study was to determine whether it could prevent amputation in these patients. Since December 1992, 53 STS patients were treated by ILP with TNF and melphalan. Thirteen patients had multifocal STS (2–50 lesions). ILP was performed via the iliac (6), femoral (1), popliteal (1), subclavian (2) or brachial (3) vessels using a low-flow technique (150–450 ml/min). Leakage was monitored with a radio-isotopic tracer. rTNF- $\alpha$  (3 and 4 mg for upper and lower limbs) and 1–1.5 mg/kg melphalan were administered into the perfusate at 39–40°C. Perfusion time was 90 min. Mortality occurred in two elderly (78–79 years) patients due to sepsis in one and aspiration pneumonia in the other. Local adverse effects included erythema (8) and blisters (4). Overall response rate was 92% (12/13). Five patients had CR (38%) and seven PR (54%). Responses were confirmed histologically by multiple biopsies. Limb salvage was achieved in 10/13 patients. Three patients required amputations due to insufficient response (1), extensive tumor necrosis (1), and neurovascular bundle involvement (1). Both patients who died had a positive response (1 CR, 1 PR) and it was assumed that had they survived, limb salvage would have occurred. Within a mean follow-up period of 16 months (4–41 months), three patients had local recurrence. Systemic disease occurred in eight patients; all died at 4–35 months. In conclusion, multifocal STS carries a poor prognosis. For this unfortunate group of patients, ILP with TNF and melphalan offers effective palliation obtained in a single procedure.

#### 45. Oncological Outcome After Unplanned Primary Excision of Soft Tissue Sarcomas Compared to Primary Adequate Resection

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Unplanned resection often is performed initially in patients suffering from soft tissue sarcomas under assumption of a benign disease. The aim of the study was to evaluate overall survival rates in patients who underwent initial unplanned resection followed by a planned resection, as compared to patients who underwent primary planned biopsy and resection. Between 1970 and 1995, 232 patients suffering from soft tissue sarcoma of the upper extremity (23%), lower extremity (64%), pelvis (11%), neck and trunk wall (2%) located epifascially (7%) and subfascially (93%) with histological grading I (13%), II (24%), and III (63%) and a mean maximum diameter of 90 mm (range, 10–300) were treated by resection, chemotherapy, and radiation therapy. Ninety-seven female and 135 male patients were evaluated in a retrospective study. In group 1, unplanned inadequate initial or repeated resec-

tion was performed in 61% of patients followed by revision surgery at our institution in a mean of 20.5 months (range, 0–241) after the first surgical intervention. In group 2, biopsy and planned adequate surgery was performed in 91 patients (39%). The histological evaluation showed intralesional resection in 91%, marginal resection in 8%, and radical resection in 1% of patients after unplanned initial resection. After planned resection, histologically radical margins were found in 20%, whereas the resection was wide in 49%, marginal in 22%, and intralesional in only 9% of the patients. After a mean follow-up of 61 months (range, 1–360), 42% of patients had died because of the disease, 26% showed no evidence of disease, 14% were continuously disease-free, 12% were alive with disease, and 7% of patients had died because of other diseases. We found a higher survival rate in patients with tumors smaller than 50 mm in diameter, low tumor grading, and after wide and marginal resection. There was no difference in the survival time between the two groups with regard to initial type of surgery. From these results we conclude that in case of adequate reexcision of a soft tissue sarcoma, in spite of a primary inadequate excision, equally good survival rates may be achieved as compared to planned biopsy and resection, although a deterioration in the functional outcome (not evaluated in this study) has to be expected after repeated resections.

#### 46. Locoregional Melanoma Recurrence in a Previously Dissected Lymph Node Basin: Contribution of Iterative Surgery

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**Background and Objectives:** The aim of this study was to examine the efficacy of a subsequent dissection in patients with locoregional melanoma recurrence.

**Methods:** Between 1984 and 1997, 183 therapeutic lymph node dissections (LNDs) for 122 patients with nodal metastasis were performed. Patients were 72 men and 50 women with a mean age of 51 years ( $\pm 15$ ). The site of the primary melanomas were extremity in 66 cases (upper: 17; lower: 49), trunk in 49 cases, others in 5 cases, and in 2 cases the site of the primary lesion was unknown. The first LNDs were as follows: axilla in 61 cases, inguinal in 41 cases, ilio-inguinal in 14 cases, ilio-inguinal and lumbo-aortic in 1 case, and others in 3 cases. In 45 cases (36.8%) a second therapeutic LND was performed for recurrence developed in the same nodal basin in which a lymphadenectomy had been performed or in continuity with the first LND with no evidence of distant metastases. LND were axilla in 20 cases, inguinal in 8 cases, ilio-inguinal in 8 cases, iliac in 7 cases, iliac and lumbo-aortic in 2 cases. Among these 45 cases, a third therapeutic LND was performed for locoregional recurrence in 12 cases (26%) (axilla in 5 cases, ilio-inguinal in 3, iliac in 1, lumbo-aortic in 1, iliac and lumbo-aortic in 2), and a fourth LND in 4 cases (axilla: 3; inguinal: 1). An enlarged resection was performed in 29 cases: in 11 cases for first LND (9%), in 11 cases for second LND (24%), in 6 cases for third LND (50%), and in 1 case for fourth LND.

**Results:** The mean numbers of nodes removed at the initial dissection were:  $12.5 \pm 7$  and  $9.2 \pm 6$ , respectively, for 77 patients with one LND only and for the 45 patients with a second LND. The mean numbers of nodes involved at the initial dissection were, respectively, for the same group,  $4.5 \pm 6$  and  $1.9 \pm 3$ . Two and five actuarial survival years after the first LND were, respectively, 56 and 22.5% for the 122 patients, 54 and 24% for the 77 patients submitted to one LND, 67 and 35% for the 45 patients submitted to a second LND, and 100 and 66% for the 12 patients submitted to a third LND.

**Conclusions:** Approached in this fashion, only a subgroup of patients will show recurrence in a previously dissected nodal basin, a few of whom can be salvaged by a second dissection, with interesting results in term of survival and local control. However, enlarged resection is frequently required.

#### 47. Cellular Immune Response to Cancervax in Patients Receiving Active Immunotherapy for Metastatic Cancers

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We previously demonstrated that immunization of stage IV melanoma patients with CancerVax elicits both cellular and humoral immune responses and significantly improves survival. CancerVax is a polyvalent vaccine developed from three melanoma cell lines expressing 15 different well-characterized immunogenic antigens. However, nine of these antigens are also found in other types of solid neoplasms. This preliminary study of CancerVax therapy for patients with metastatic nonmelanoma solid tumors (10 soft tissue sarcoma, 13 gastrointestinal, 6 lung, and 10 other carcinomas) examines the survival impact of a cellular immune response to CancerVax, defined by delayed-type hypersensitivity (DTH) to intradermal injection of the vaccine. Patients were evaluated for DTH to CancerVax at 0, 2, 4, 8, 12, and 16 weeks of vaccine therapy. CancerVax at one-tenth of a vaccine dose was injected intradermally on the forearm. The DTH response was measured in millimeters of induration 48 hr after injection. A positive response was defined as  $\geq 10$ -mm induration if initial induration was  $< 10$  mm at week 0, or induration greater than initial induration if initial induration was  $\geq 10$  mm at week 0. Overall, 20/39 patients (51%) had a significant DTH response to CancerVax. Although statistically not quite significant ( $P = 0.087$ ), their median survival was 40 months, compared to 17.5 months for those patients who did not respond immunologically. These preliminary findings indicate that CancerVax can elicit a cellular immune response in patients with metastatic solid neoplasms and may be associated with improved survival.

#### 48. Five-Year Survival in Malignant Melanoma Before and After the Availability of CT and MRI Surveillance

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**Background and Objectives:** The development of modern scanning techniques in the early 1980s provided clinical tools for earlier detection of metastatic disease in patients diagnosed with malignant melanoma. Early detection and intervention in patients with metastatic disease offered promise for improvement in long-term survival. Follow-up is now available to assess changes in clinical outcome before and after the introduction of modern scanning techniques. This study describes a matched-pair analysis of survival in melanoma patients before and after surveillance with computed tomography (CT) and magnetic resonance imaging (MRI).

**Methods:** We performed a matched cohort comparison of clinical stage I and II melanoma patients treated between 1971 and 1981 (group 1) and between 1982 and 1992 (group 2). Patients receiving our melanoma vaccine were excluded. All patients underwent elective (25%) or therapeutic (75%) lymph node dissection, and all had pathologically positive lymph nodes (AJCC stage III). Cohort matching was constructed using the clinical parameters of primary site, Breslow depth, clinical stage, number of positive lymph nodes, and age. A total of 204 matched pairs were identified. Estimated 5-year survival rates within groups 1 and 2 were calculated. Statistical analysis was used to determine significant differences in estimated 5-year survival rate.

**Results:** Estimated 5-year survival rate was  $44\% \pm 7\%$  in group 1 and  $43\% \pm 6\%$  in group 2, not a statistically significant difference ( $P = 0.63$ ).

**Conclusions:** The 5-year survival rate of AJCC stage III melanoma patients has not been altered by modern scanning techniques for early detection of metastatic disease. This suggests that routine MRI and CT surveillance for malignant melanoma may not be cost-effective until more potent therapeutic modalities are widely available.

#### 49. Large Melanoma: Retrospective Analysis of Treatment

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**Background and Objectives:** Treatment of large melanoma (LM) is still controversial and not successful enough. Therefore a question arises: How to start the treatment?

**Methods:** The results of different scheme of treatment were evaluated in 140 patients with primary cutaneous melanoma T4NO-2MO-1a for the 1988–1995 period. Eighty-one patients were treated by wide excision (WE) with regional lymphadenectomy (RLE, 38 patients) and following i.v. chemotherapy (ChT, 45 patients). Another 48 patients had preoperative radiotherapy (PRT) on LM ( $25.5 \pm 3.5$  Gy) with next WE, RLE (34 patients), and ChT (39 patients). Thirty-one patients of third group had only local radiotherapy (70–80 Gy), ChT, or supportive treatment. Generally, 108 patients had tumor more than 10 mm in thickness.

**Results:** Treatment of LM was palliative from the very beginning in spite of a combination of the surgical methods with radiotherapy or chemotherapy, because LM at that time already was at the stage of systemic disease. Nobody survived 3 years with melanoma more than 3 cm thick. Large melanoma is uncontrolled by local preoperative radiotherapy or by postoperative i.v. ChT.

**Conclusions:** We have therefore proposed the new treatment sequence for primary LM: first, neoadjuvant endolymphatic (EL) i.v. chemotherapy 2–3 cycles and biotherapy (Interferon); second, radiation therapy (simultaneously with ChT) 75–80 Gy on tumor site and 40–45 Gy on lymph nodal metastases, N1; third, surgical removal of tumor with RLE; and fourth, postoperative cycles of combination EL, i.v. ChT, and biotherapy for 2 years.

## 50. Survival of Patients With Melanoma of the Lower Extremity Decreases With Distance From the Trunk

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Early stage melanoma of the lower extremity carries a favorable prognosis. However, several small retrospective studies have suggested that melanoma located in the foot portends a poor prognosis. We hypothesized that the exact location of a primary melanoma on the lower extremity has prognostic importance. From our 8,000-patient melanoma database we identified 673 AJCC stage I and II patients seen at our institution between 1 January 1971 and 31 December 1991, all within 3 months after diagnosis of a primary melanoma on the foot ( $n = 98$ ), calf ( $n = 347$ ), or thigh ( $n = 228$ ). Survival curves were estimated by the Kaplan-Meier method. Statistical analysis was performed by log rank test for univariate and Cox proportional hazard regression for multivariate analysis. On univariate analysis, location of the primary in the leg, gender, Breslow depth, Clark level, and age at diagnosis were each significant for overall survival (OS) and disease-free survival (DFS) ( $P = 0.0001$ ). On multivariate analysis, location of the primary was confirmed as an independent prognostic variable for OS ( $P = 0.0003$ ) and DFS ( $P = 0.0013$ ). When all three groups were compared, 5-year rates of OS and DFS were lowest for foot primaries (75.7% and 70.7%, respectively), intermediate for calf primaries (93% and 89%), and highest for thigh primaries (97% and 95%). Thus, the prognosis for patients with primary melanomas of the lower extremity depends on proximity to the trunk, with foot lesions being the highest risk. This difference should be considered when stratifying patients for treatment.

## 51. A New Prognostic System for Hepatocellular Carcinoma: Results From the CLIP-03 Retrospective Study

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**Background and Objectives:** The clinical outcome of cirrhotic patients with hepatocellular carcinoma depends both on the residual liver function and tumor characteristics. However, the relative prognostic weight of these variables is not well defined. The aims of this study were to verify the value of known prognostic factors and to devise a prognostic index (CLIP score) more sensitive than the commonly used Okuda staging system.

**Methods:** A retrospective analysis was performed of the cases of hepatocellular carcinoma diagnosed at 16 Italian institutions from 1990 to 1992. Overall survival was the only end point used in the analysis. Univariate survival curves were estimated using the Kaplan-Meier method and compared by means of the log rank test. The Cox model was used for multivariate analyses.

**Results:** Four hundred thirty-five cases of hepatocellular carcinoma were collected. As of January 97, 313 patients (72%) were deceased. Overall median survival was 20 months. Independent predictive factors of shorter survival by Cox model were child stage, tumor morphology, alpha-fetoprotein, and portal vein thrombosis. Based on this best-fitting model, a CLIP score was produced, assigning simple scores (0/1/2) to the covariates. Compared to the Okuda stage, the CLIP score defines one-third of patients with an impressively more favorable prognosis and one-fifth with a relatively shorter life expectancy.

**Conclusions:** The CLIP score is a new staging system that accounts for both liver function and tumor characteristics. It is easy to calculate and appears to give more prognostic information than the Okuda stage. As the CLIP score has been produced on a retrospective series, a prospective validation is required.

## 52. Management of Malignant Liver Tumors (MLT) Hepatoblastoma (HB) and Hepatocellular Carcinoma (HCC) in Children

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**Background and Objectives:** Malignant liver tumors (MLT) make up 1% of all solid tumors in the pediatric age group. Effective chemotherapy introduced in the 1970s has dramatically improved survival in HB, less so in HCC. In the first international multidisciplinary multiinstitutional trial called SIOPEL I, preoperative chemotherapy was given to all patients. The rationale for this treatment was that the operation would be easier, less hazardous, and there should be less risk for residual disease. A new anatomically based system for describing the pretreatment extent of disease (PRETEXT) was introduced and will be described. The major trials in the United States from POG, CCSG, as well as a national German study advocate primary surgery.

**Methods:** In this, the first trial (SIOPEL I), the new strategy was for all patients to receive preoperative chemotherapy PLADO, i.e., CisPlatinum and Doxorubicin (Cisplatinum 80 mg/m<sup>2</sup> i.v. over 24 hr + Doxorubicin 60 mg/m<sup>2</sup> over 48 hr, every 21 days, 6 courses). Pretreatment biopsy was recommended. Aims were to study the feasibility toxicity and outcome of children with HB and HC. Pretreatment extent of disease was recorded (PRETEXT I-IV). Strategies are based on the results of the First International (SIOP) Trial SIOPEL III 1990-1994, SIOPEL II PILOT 1995-1997, and rationale for the future SIOPEL III.

**Results:** One hundred fifty-four patients with HB and 40 with HC were registered from 91 centers in 31 countries. In the 154 patients with HB, the overall survival is 81% event-free survival 67% (2 years median follow-up); 20% presented with metastases and in these event-free survival was 32%, which is better than in other studies. Thirteen had a liver transplantation and seven are ANED. For HCC overall survival is 41%; and event-free survival 28%. During the 4 years of the study, 138 of the 154 HB had preoperative chemotherapy. The response rate in these was 84%, the resectability rate 76%, and the relapse rate 6%. The toxicity was within reasonable limits. A multivariate analysis in HB showed that metastatic disease, PRETEXT IV (all four sectors of liver involved), and extrahepatic disease were poor prognostic factors defining a high-risk group of patients.

**Conclusions:** From SIOPEL I, preoperative chemotherapy, PLADO is effective and the results justify this approach. Toxicity of PLADO is acceptable. In the next-generation feasibility study for HB (SIOPEL II Pilot), treatment was stratified according to risk groups. The aim was to reduce therapy in the low risk and intensify therapy in the high risk (low risk is single-agent Cisplatin; high risk, Carboplatin added to PLADO). Forty patients with HB have been registered and although the results are still blinded, preliminary analysis show that this approach is feasible. In SIOPEL III for HB (to be activated in September 1997), a randomized study in the low-risk patients is proposed. Randomization is to be between the monotherapy Cisplatin and PLADO. The high-risk group will receive the intensified therapy in a one-arm study.



### 53. Factors Influencing Survival After Resection for Ductal Adenocarcinoma of the Head of the Pancreas

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Recent reports have demonstrated a reduction in the morbidity and mortality of pancreatic resection and improvement in the 5-year actuarial survival for patients with resected ductal adenocarcinoma. The purpose of this study was to determine the factors favoring long-term survival after pancreatoduodenectomy. Between 1974 and 1997, 336 patients with pancreatic carcinoma, including 235 patients with pancreatic head tumors, were evaluated and treated at our department. Seventy-five (32%) patients with pancreatic head carcinoma underwent pancreatoduodenectomy, their ages ranged from 40 to 76 years, with a mean age of 61 years. Fifty patients were male; 25 were female. The overall postoperative mortality rate was 5.3% (four patients) and morbidity was 25%. Median survival following resection was 16 months (range, 0–79%). The estimated 1-, 2-, and 5-year survival were 68%, 46%, and 18.6%, respectively. There were 14 5-year survivors. Of the 75 patients, 24 (32%) had negative lymph nodes. The median and 5-year survivals in these node-negative patients were 24 months (range, 5–79) and 41% (10 patients), respectively, whereas the median survival and 5-year survivals in 51 patients with lymph node metastases were 11 months (range, 0–61) and 8% (4 patients), respectively. As expected, margin status of the operation specimen also proved to be a highly significant factor predicting survival. Patients resected with negative margins (curative resections,  $n = 60$ ) had an actuarial 5-year survival rate of 22%, with median survival of 18 months, whereas those with positive margins (palliative resections,  $n = 15$ ) fared significantly worse: their median survival was 9 months and none survived at 5 years. The diameter of the tumor was also an important predictor of survival. Of 67 patients for whom this measurement was available, 33 (49%) had tumors less than 3 cm in diameter. Median and 5-year survivals in these patients were 18 months and 30% (10 patients). When the tumor diameter exceeded 3 cm, the 5-year survival fell to 6%. Median tumor size was 3.8 cm (range, 1.0–12 cm, mean, 4.0). Pancreatoduodenectomy could be performed with low operative mortality. Lymph node metastases were found in 68% of patients undergoing resection. Pancreatoduodenectomy offered good palliation for patients with lymph node metastases and encouraging long-term survival rates as well as a chance for cure in patients with negative lymph nodes and negative margins of resection.

### 54. Diagnosis and Treatment of Hilar Cholangiocarcinoma

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**Background and Objectives:** Extension of a hilar cholangiocarcinoma (Klatskin tumor) to the left and right hepatic ducts may limit surgical access and compromise complete resection. An accurate preoperative radiological diagnosis is therefore essential.

**Methods:** This is a retrospective study in a tertiary-care center. Between January 1991 and March 1997, 68 patients were analyzed because of the differential diagnosis of hilar cholangiocarcinoma. Eventually, 43 patients were diagnosed as having a Klatskin tumor: 26 men and 17 women (median age, 63 years; range, 25–87 years). The other patients ( $n = 25$ ) were found to have either gallbladder carcinoma (3), pancreatic cancer (5), distal cholangiocarcinoma (8), metastases (2), or progressive disease without additional analysis (7).

**Results:** Ultrasonography (US) was found to be superior to CT in characterization of hilar lesions and their extension to left and right hepatic ducts as well as surrounding tissues (81% echo vs. 50% CT;  $P < 0.05$ ). Percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP) were comparable in diagnosing central lesions with both a 100% detection rate. PTC proved to be more successful and accurate to outline the entire intrahepatic biliary tree on both left and right sides compared to ERCP and ultrasonography (82% PTC vs. 37% ERCP vs. 21% US). PTC was also most effective in detection of intrahepatic tumor extension (21% PTC vs. 11% ERCP vs. 14% US vs. 13% CT). Guided by preoperative imaging, 20 patients out of 43 underwent explorative laparotomy. At laparotomy, disseminated tumor was identified in six patients (30%). Fourteen underwent surgical resection. Eventually histological examination of resection specimens showed five patients (36%) to have had a complete resection.

**Conclusions:** In our center, ultrasonography and PTC are the most useful and accurate techniques to determine resectability of hilar cholangiocarcinoma. Newer techniques such as endoluminal ultrasonography and MRCP may further improve the accuracy of preoperative staging and selection of patients for resection.